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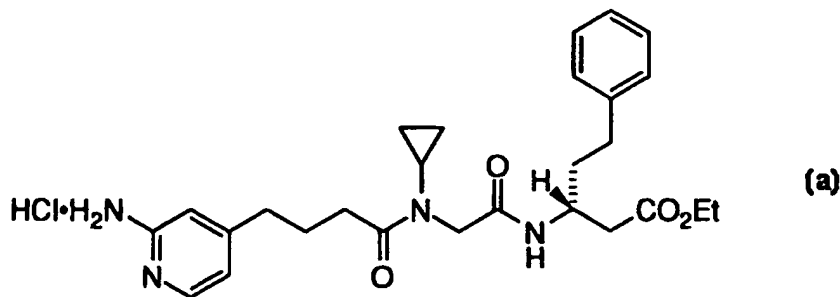
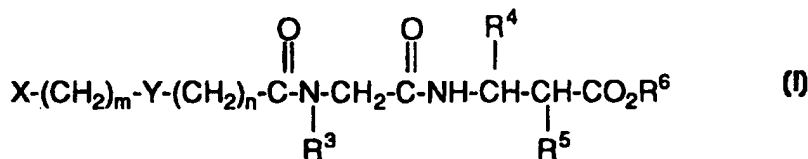
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International Bureau



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(54) Title: INTEGRIN RECEPTOR ANTAGONISTS



(57) Abstract

Fibrinogen receptor antagonists having formula (I), for example (a), which are useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets.

FOR THE PURPOSES OF INFORMATION ONLY

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TITLE OF THE INVENTION
INTEGRIN RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

5 The invention relates generally to modulating cell adhesion and to inhibiting the binding of fibrinogen and other proteins to blood platelets, and inhibiting the aggregation of blood platelets specifically to the gp IIb/IIIa fibrinogen receptor site. Fibrinogen is a glycoprotein present in blood plasma that participates in platelet aggregation and in
10 fibrin formation. Platelets are cell-like anucleated fragments, found in the blood of all mammals, that also participate in blood coagulation. Interaction of fibrinogen with the IIb/IIIa receptor site is known to be essential for normal platelet function.

 When a blood vessel is damaged by an injury or other
15 causative factor, platelets adhere to the disrupted subendothelial surface. The adherent platelets subsequently release biologically active constituents and aggregate. Aggregation is initiated by the binding of agonists, such as thrombin, epinephrine, or ADP to specific platelet membrane receptors. Stimulation by agonists results in exposure of
20 latent fibrinogen receptors on the platelet surface, and binding of fibrinogen to the glycoprotein IIb/IIIa receptor complex.

 Attempts have been made to use natural products and synthetic peptides to determine the mechanism of adhesion and platelet aggregation. For example, Rouslahti and Pierschbacher in *Science*, 238,
25 491-497 (1987), describe adhesive proteins such as fibronectin, vitronectin, osteopontin, collagens, thrombospondin, fibrinogen, and von Willebrand factor that are present in extracellular matrices and in blood. The proteins contain the tripeptide arginine-glycine-aspartic acid (RGD) as their glycoprotein IIb/IIIa recognition site. These arginine-
30 glycine-aspartic acid containing tripeptides are recognized by at least one member of a family of structurally related receptors, integrins, which are heterodimeric proteins with two membrane-spanning subunits. The authors state that the conformation of the tripeptide

- 2 -

sequence in the individual proteins may be critical to recognition specificity.

Cheresh in *Proc. Nat'l Acad. Sci. U.S.A.*, 84, 6471-6475, (1987), describes an Arg-Gly-Asp directed adhesion receptor expressed
5 by human endothelial cells that is structurally similar to the IIb/IIIa complex on platelets but is antigenically and functionally distinct. This receptor is directly involved in endothelial cell attachment to fibrinogen, von Willebrand factor, and vitronectin.

Pierschbacher and Rouslahti, in *J. of Biol. Chem.*, 262, (36), 17294-17298 (1987) hypothesized that the Arg-Gly-Asp sequence
10 alone would be a sufficient signal for receptor recognition and binding and that, therefore, the conformation of the tri-peptide sequence would be determinative. Various synthetic peptides were produced and the authors concluded that the stereochemical conformation of Arg-Gly-Asp
15 as influenced by enantiomeric substitutions or additions to this sequence significantly influenced receptor-ligand interaction. The authors further showed that cyclization of a decapeptide by forming a disulfide bridge between non-terminal residues Pen and Cys, rendered the peptide much less effective at inhibiting attachment to fibronectin.

20 In *Proc. Nat'l Acad. Sci. U.S.A.*, 81, 5985-5988 (1984), the same authors describe tetrapeptide variants of the cell recognition site of fibronectin that retain attachment-promoting activity. Peptides having a tetrapeptide recognition site are described in U.S. Pat. Nos. 4,589,881 and 4,614,517. A number of large polypeptide fragments in the cell-
25 binding domain of fibronectin have cell-attachment activity. For example, see U.S. Pat. Nos. 4,517,686, 4,661,111 and U.S. Pat. No. 4,578,079.

Ruggeri *et al.*, *Proc. Nat'l Acad. Sci. U.S.A.*, 83, 5708-5712 (1986) explore a series of synthetic peptides designed in lengths to
30 16 residues, that contain RGD and a valine attached to the aspartic acid residue of RGD that inhibit fibrinogen binding to platelets. See also Koczewiak *et al.*, *Biochem.*, 23, 1767-1774 (1984); Ginsberg *et al.*,

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J. Biol. Chem., 260(7), 3931-3936 (1985); and Haverstick *et al.*, *Blood*, 66(4), 946-952 (1985). Other inhibitors are disclosed in Eur. Pat. App. Nos. 275,748 and 298,820.

- A number of low molecular weight polypeptide factors
- 5 have been isolated from snake venom. These factors apparently have high affinity for the gp IIb/IIIa complex. For example, Huang *et al.*, *J. Biol. Chem.*, 262, 16157-16163 (1987); Huang *et al.*, *Biochemistry*, 28, 661-666 (1989) describe the primary structure of the venom trigramin which is a 72 amino acid polypeptide that contains the RGD subunit.
- 10 Echistatin is another compound which has high affinity for the gp IIb/IIIa complex. This polypeptide contains 49 amino acids and has the RGD subunit and various disulfide bridges. Gan *et al.*, *J. Biol. Chem.*, 263, 19827-19832 (1988). See also, Dennis *et al.*, *Proc. Nat'l Acad. Sci. USA*, 87, 2471-2475 (1989). However, these snake venom factors also
- 15 have high affinity for other members of the adhesive protein receptor family including the vitronectin and fibronectin receptors so are not selective for the gp IIb/IIIa complex.

- While it is known that the tripeptide sequence Arg-Gly-Asp is present in certain polypeptides that can duplicate or inhibit the cell
- 20 attachment-promoting effects of fibronectin and vitronectin, the tripeptide Arg-Gly-Asp has low activity. At present, there is little understanding of how other amino acids coupled to this sequence influence binding specificity. U.S. Pat. No 5,023,233, assigned to Merck & Co., Inc., discloses small cyclic hexapeptides which contain the
- 25 sequence Arg-Gly-Asp and are useful platelet aggregation inhibitors. U.S. Pat. No. 5,037,808 discloses the use of indolyl platelet-aggregation inhibitors which are believed to act by antagonizing interactions between fibrinogen and/or extracellular matrix proteins and the platelet gp IIb/IIIa receptor. U.S. Pat. No. 5,037,808 discloses guanidino peptide
- 30 mimetic compounds that retain an Asp residue which inhibit platelet aggregation. The application PCT/US90/02746 describes the use of antibody-poly-peptide conjugates wherein said polypeptides contain the Arg-Gly-Asp (RGD) sequence.

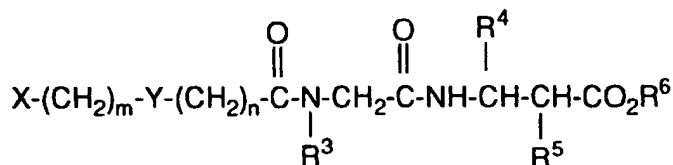
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The application PCT/US91/00564 discloses the use of large cyclic peptides containing RGD flanked by proline residues which are platelet aggregation inhibitors. The application PCT/US90/03788 discloses small cyclic platelet aggregation inhibitors which are synthetic cyclic pentapeptides containing the tripeptide sequence Arg-Gly-Asp and a thioether linkage in the cycle. The application PCT/US90/05367 published May 2, 1991 also discloses the use of peptides and pseudopeptides such as N-amidino-piperidine-3-carboxylglycyl-L-aspartyl-L-valine that inhibit platelet aggregation and thrombus formation in mammalian blood. The application Eur. Pat. App. No. 91103462.7 discloses linear compounds which can include internal piperazinyl or piperidinyl derivatives. Eur. Pat. App. No. 91300179.8, assigned to Merck & Co., Inc., and published on July 17, 1991 discloses linear polypeptide fibrinogen receptor antagonists. Eur. Pat. App. No. 90101404.3 discloses compounds of the $R^1-A-(W)_a-X-(CH_2)_b-(Y)_c-B-Z-COOR$ wherein R^1 is a guanidino or amidino moiety and A and B are chosen from specific monosubstituted aryl or heterocyclic moieties.

While a multitude of compounds or peptide analogs believed to inhibit platelet aggregation by inhibiting binding to a blood platelet by fibrinogen are known, the present invention provides novel fibrinogen receptor antagonists that have significant binding activity and are, therefore, useful for the reasons stated herein. A number of very serious diseases and disorders involve hyperthrombotic complications which lead to intravascular thrombi and emboli. Myocardial infarction, stroke, phlebitis and a number of other serious conditions create the need for novel and effective fibrinogen receptor antagonists.

SUMMARY OF THE INVENTION

The invention is a compound of the formula:



30

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and pharmaceutically acceptable salts thereof, wherein

X is

5 a 5- or 6-membered monocyclic aromatic ring system containing
0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either
unsubstituted or substituted with R¹ or R², or

10 a 9- to 10-membered polycyclic ring system, wherein one or
more of the rings is aromatic, containing 0, 1, 2, 3 or 4
heteroatoms selected from N, O and S and either
unsubstituted or substituted with R¹ or R²,

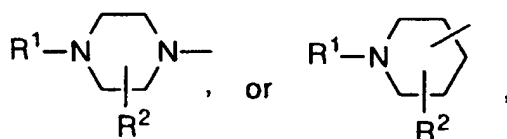
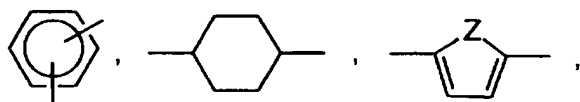
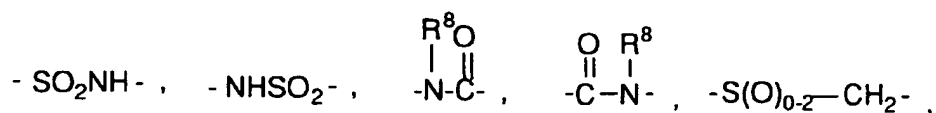
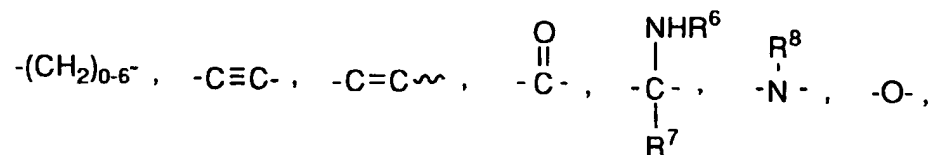
wherein R¹ and R² are independently selected from the group
consisting of

15 hydrogen, F, Cl, Br, I,
C₁-10 alkyl,
C₃-8 cycloalkyl,
aryl,
aryl C₁-8 alkyl,
amino,
20 amino C₁-8 alkyl,
C₁-3 acylamino,
C₁-3 acylamino C₁-8 alkyl,
C₁-6 alkylamino,
C₁-6 alkylamino C₁-8 alkyl,
25 C₁-6 dialkylamino,
C₁-6 dialkylamino C₁-8 alkyl,
C₁-4 alkoxy,
C₁-4 alkoxy C₁-6 alkyl,
carboxy,
30 carboxy C₁-6 alkyl,
C₁-3 alkoxycarbonyl,
C₁-3 alkoxycarbonyl C₁-6 alkyl,
carboxy C₁-6 alkyloxy and

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hydroxy,
hydroxy C₁-6 alkyl;

Y is



5 where Z is O, NR⁸, or S; and R⁸ is defined as R¹ above;

R³ and R⁴ are independently

hydrogen,

a five or six membered mono or polycyclic aromatic ring system

containing 0, 1, 2, 3, or 4 heteroatoms selected from

10 nitrogen, oxygen and sulfur, either unsubstituted or

substituted, with one or more groups selected from

hydroxyl, halogen, cyano, trifluoromethyl, C₁-3 alkoxy,

C₁-5 alkylcarbonyloxy, C₁-5 alkoxy carbonyl, C₁-5 alkyl,

aminoC₁-5 alkyl, hydroxycarbonyl, hydroxycarbonylC₁-5

15 alkyl, or hydroxycarbonylC₁-5 alkoxy,

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5 -(CH₂)_n-aryl, wherein n=1-4 and aryl is defined as a five or six
 membered mono or polycyclic aromatic ring system
 containing 0, 1, 2, 3, or 4 heteroatoms selected from
 nitrogen, oxygen and sulfur, either unsubstituted or
10 substituted, with one or more groups selected from
 hydroxyl, halogen, cyano, trifluoromethyl, C₁-3 alkoxy,
 C₁-5 alkylcarbonyloxy, C₁-5 alkoxy carbonyl, C₁-5 alkyl,
 aminoC₁-5 alkyl, hydroxycarbonyl, hydroxycarbonylC₁-5
 alkyl, or hydroxycarbonylC₁-5 alkoxy,
15 halogen,
 hydroxyl,
 C₁-5 alkylcarbonylamino,
 arylC₁-5 alkoxy,
 C₁-5 alkoxy carbonyl,
20 aminocarbonyl,
 C₁-5 alkylaminocarbonyl,
 C₁-5 alkylcarbonyloxy,
 C₃-8 cycloalkyl,
 oxo,
25 amino,
 C₁-3 alkylamino,
 aminoC₁-3 alkyl,
 arylaminocarbonyl,
 arylC₁-5 alkylaminocarbonyl,
30 aminocarbonyl,
 aminocarbonyl-C₁-4 alkyl,
 hydroxycarbonyl,
 hydroxycarbonyl C₁-5 alkyl,
 C₁-6 alkyl, either unsubstituted or substituted, with one or more
 groups selected from halogen, hydroxyl,
 C₁-5 alkylcarbonylamino, arylC₁-5 alkoxy,
 C₁-5 alkoxy carbonyl, aminocarbonyl,
 C₁-5 alkylaminocarbonyl,
 C₁-5 alkylcarbonyloxy, C₃-8 cycloalkyl, oxo, amino,

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- 5 C₁-3 alkylamino, aminoC₁-3 alkyl,
arylamino, arylC₁-5alkylaminocarbonyl,
aminocarbonyl, aminocarbonyl-C₁-4 alkyl,
hydroxycarbonyl, or hydroxycarbonyl C₁-5 alkyl,
provided that the carbon atom to which R³ and R⁴ are
attached bears only one heteroatom,
- 10 -(CH₂)_m C≡CH,
-(CH₂)_m C≡C-C₁-6 alkyl,
-(CH₂)_m C≡C-C₃-7cycloalkyl,
-(CH₂)_m C≡C- aryl,
-(CH₂)_m C≡C-C₁-6 alkyl aryl,
-(CH₂)_m CH=CH₂,
-(CH₂)_m CH=CH C₁-6 alkyl,
-(CH₂)_m CH=CH-C₃-7cycloalkyl,
15 -(CH₂)_m CH=CH aryl,
-(CH₂)_m CH=CH C₁-6 alkyl aryl,
-(CH₂)_m SO₂C₁-6 alkyl, or
-(CH₂)_m SO₂C₁-6 alkylaryl;
- 20 R⁵ is
hydrogen,
fluorine,
C₁-8 alkyl,
hydroxyl,
25 hydroxy C₁-6 alkyl,
carboxy,
carboxy C₁-6 alkyl,
C₁-6 alkyloxy.
C₃-8 cycloalkyl,
30 aryl C₁-6 alkyloxy,
aryl,
aryl C₁-6 alkyl,
C₁-6 alkylcarbonyloxy,
amino,

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- amino C₁₋₆ alkyl,
C₁₋₆ alkylamino,
C₁₋₆ alkylamino C₁₋₆ alkyl,
aryl amino,
5 aryl amino C₁₋₆ alkyl,
aryl C₁₋₆ alkylamino,
aryl C₁₋₆ alkylamino C₁₋₆ alkyl,
aryl carbonyloxy,
aryl C₁₋₆ alkylcarbonyloxy,
10 C₁₋₆ dialkylamino,
C₁₋₆ dialkylamino C₁₋₆ alkyl,
C₁₋₆ alkylaminocarbonyloxy,
C₁₋₈ alkylsulfonylamino,
C₁₋₈ alkylsulfonylamino C₁₋₆ alkyl,
15 aryl sulfonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylsulfonylamino,
aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
C₁₋₈ alkyloxycarbonylamino,
C₁₋₈ alkyloxycarbonylamino C₁₋₈ alkyl,
20 aryl oxycarbonylamino C₁₋₈ alkyl,
aryl C₁₋₈ alkyloxycarbonylamino,
aryl C₁₋₈ alkyloxycarbonylamino C₁₋₈ alkyl,
C₁₋₈ alkylcarbonylamino,
C₁₋₈ alkylcarbonylamino C₁₋₆ alkyl,
25 aryl carbonylamino C₁₋₆ alkyl,
aryl C₁₋₆ alkylcarbonylamino,
aryl C₁₋₆ alkylcarbonylamino C₁₋₆ alkyl,
aminocarbonylamino C₁₋₆ alkyl,
C₁₋₈ alkylaminocarbonylamino,
30 C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
aryl aminocarbonylamino C₁₋₆ alkyl,
aryl C₁₋₈ alkylaminocarbonylamino,
aryl C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
aminosulfonylamino C₁₋₆ alkyl,

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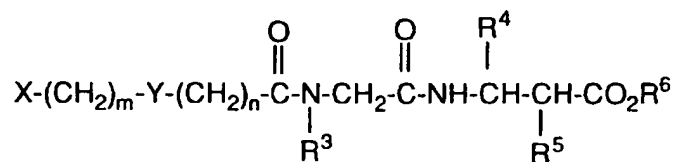
- C₁-8 alkylaminosulfonylamino,
C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino C₁-6 alkyl,
aryl C₁-8 alkylaminosulfonylamino,
5 aryl C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
C₁-6 alkylsulfonyl,
C₁-6 alkylsulfonyl C₁-6alkyl,
aryl sulfonyl C₁-6alkyl,
aryl C₁-6 alkylsulfonyl,
10 aryl C₁-6 alkylsulfonyl C₁-6alkyl,
C₁-6 alkylcarbonyl,
C₁-6 alkylcarbonyl C₁-6 alkyl,
aryl carbonyl C₁-6alkyl,
aryl C₁-6 alkylcarbonyl,
15 aryl C₁-6 alkylcarbonyl C₁-6alkyl,
C₁-6 alkylthiocarbonylamino,
C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
aryl thiocarbonylamino C₁-6 alkyl,
aryl C₁-6 alkylthiocarbonylamino,
20 aryl C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
aminocarbonyl C₁-6 alkyl, or
C₁-8 alkylaminocarbonyl, or
C₁-8 alkylaminocarbonyl C₁-6 alkyl, or
aryl aminocarbonyl C₁-6 alkyl,
25 aryl C₁-8 alkylaminocarbonyl,
aryl C₁-8 alkylaminocarbonyl C₁-6 alkyl,
wherein alkyl groups and aryl groups may be unsubstituted or
substituted with one or more substituents selected from R¹ and R²; and
- 30 R⁶ and R⁷ are independently
hydrogen,
C₁-8 alkyl,
aryl,
aryl C₁-8 alkyl,

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- hydroxy,
 C₁-8 alkyloxy,
 aryloxy,
 aryl C₁-6 alkyloxy,
 5 C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 aryl C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 C₁-8 alkylaminocarbonylmethyleneoxy, or
 C₁-8 dialkylaminocarbonylmethyleneoxy
 where m and n are integers 0-6.

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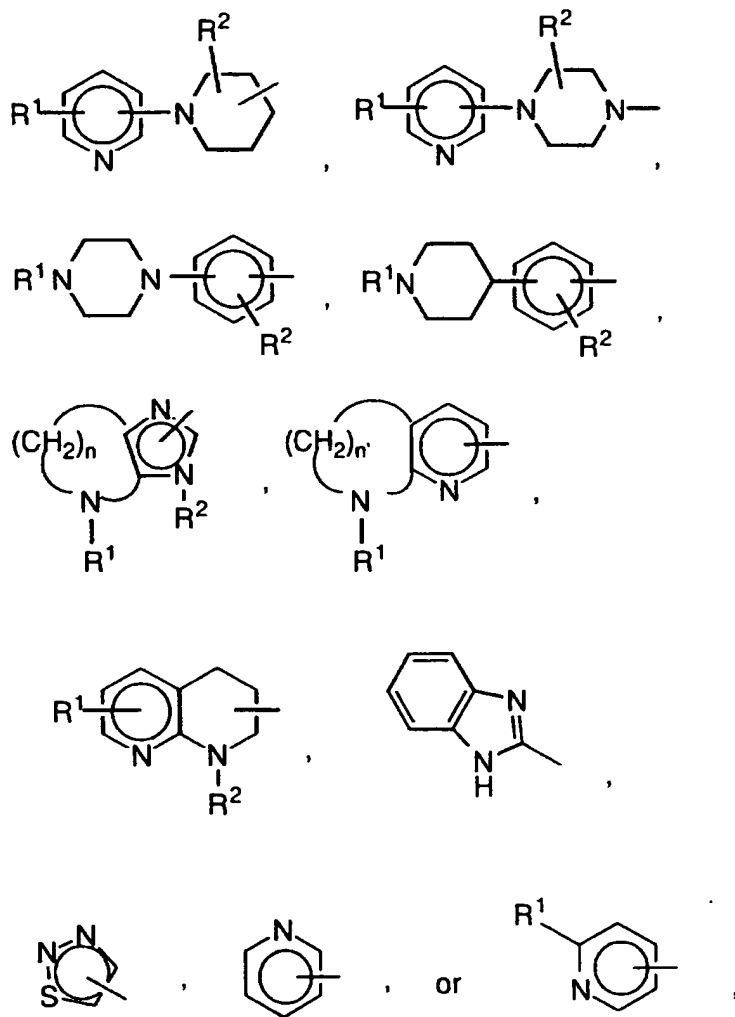
In a class of compounds of the invention are compounds of the formula:



and pharmaceutically acceptable salts thereof, wherein

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X is



5

wherein n is 2-4, and n' is 2 or 3, and
 wherein R^1 and R^2 are independently selected from the group
 consisting of

10

hydrogen, F, Cl, Br, I,
 C1-10 alkyl,
 C3-8 cycloalkyl,
 aryl,
 aryl C1-8 alkyl,

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5 amino,
amino C₁₋₈ alkyl,
C₁₋₃ acylamino,
C₁₋₃ acylamino C₁₋₈ alkyl,
C₁₋₆ alkylamino,
C₁₋₆ alkylamino C₁₋₈ alkyl,
C₁₋₆ dialkylamino,
C₁₋₆ dialkylamino C₁₋₈ alkyl,
10 C₁₋₄ alkoxy,
C₁₋₄ alkoxy C₁₋₆ alkyl,
carboxy,
carboxy C₁₋₆ alkyl,
C₁₋₃ alkoxy carbonyl,
C₁₋₃ alkoxy carbonyl C₁₋₆ alkyl,
15 carboxy C₁₋₆ alkyloxy and
hydroxy,
hydroxy C₁₋₆ alkyl;

R⁵ is
20 hydrogen,
fluorine,
C₁₋₈ alkyl,
hydroxyl,
hydroxy C₁₋₆ alkyl,
25 carboxy,
carboxy C₁₋₆ alkyl,
C₁₋₆ alkyloxy.
C₃₋₈ cycloalkyl,
aryl C₁₋₆ alkyloxy,
30 aryl,
aryl C₁₋₆ alkyl,
C₁₋₆ alkylcarbonyloxy,
amino,
C₁₋₆ alkylamino,

- 14 -

- amino C₁-6 alkyl,
C₁-6 alkylamino C₁-6 alkyl,
aryl amino,
aryl amino C₁-6 alkyl,
5 aryl C₁-6 alkylamino,
aryl C₁-6 alkylamino C₁-6 alkyl,
aryl carbonyloxy,
aryl C₁-6 alkylcarbonyloxy,
C₁-6 dialkylamino,
10 C₁-6 dialkylamino C₁-6 alkyl,
C₁-6 alkylaminocarbonyloxy,
C₁-8 alkylsulfonylamino,
C₁-8 alkylsulfonylamino C₁-6 alkyl,
aryl sulfonylamino C₁-6 alkyl,
15 aryl sulfonylamino,
aryl C₁-6 alkylsulfonylamino,
aryl C₁-6 alkylsulfonylamino C₁-6 alkyl,
C₁-8 alkyloxycarbonylamino,
C₁-8 alkyloxycarbonylamino C₁-8 alkyl,
20 aryl C₁-8 alkyloxycarbonylamino,
aryl oxycarbonylamino,
aryl oxycarbonylamino C₁-8 alkyl,
aryl C₁-8 alkyloxycarbonylamino C₁-8 alkyl,
C₁-8 alkylcarbonylamino,
25 C₁-8 alkylcarbonylamino C₁-6 alkyl,
aryl carbonylamino C₁-6 alkyl,
aryl carbonylamino,
aryl C₁-6 alkylcarbonylamino,
aryl C₁-6 alkylcarbonylamino C₁-6 alkyl,
30 C₁-8 alkylaminocarbonylamino,
aminocarbonylamino,
aminocarbonylamino C₁-6 alkyl,
C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
aryl aminocarbonylamino C₁-6 alkyl,

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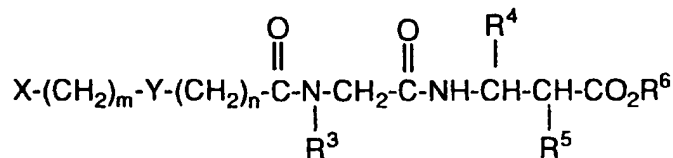
- aryl aminocarbonylamino,
aryl C₁-8 alkylaminocarbonylamino,
aryl C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
aminosulfonylamino C₁-6 alkyl,
5 aminosulfonylamino,
C₁-8 alkylaminosulfonylamino,
C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino,
10 aryl C₁-8 alkylaminosulfonylamino,
aryl C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
C₁-6 alkylsulfonyl,
C₁-6 alkylsulfonyl C₁-6alkyl,
aryl sulfonyl,
15 aryl sulfonyl C₁-6alkyl,
aryl alkylsulfonyl,
aryl C₁-6 alkylsulfonyl,
aryl C₁-6 alkylsulfonyl C₁-6alkyl,
C₁-6 alkylcarbonyl,
20 C₁-6 alkylcarbonyl C₁-6 alkyl,
aryl carbonyl C₁-6alkyl,
aryl carbonyl,
aryl C₁-6 alkylcarbonyl,
aryl C₁-6 alkylcarbonyl C₁-6alkyl,
25 C₁-6 alkylthiocarbonylamino,
C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
aryl thiocarbonylamino C₁-6 alkyl,
aryl thiocarbonylamino,
aryl C₁-6 alkylthiocarbonylamino,
30 aryl C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
aminocarbonyl C₁-6 alkyl,
aminocarbonyl,
C₁-8 alkylaminocarbonyl,
C₁-8 alkylaminocarbonyl C₁-6 alkyl,

- 16 -

- aryl aminocarbonyl C₁-6 alkyl,
 aryl aminocarbonyl,
 aryl C₁-8 alkylaminocarbonyl,
 aryl C₁-8 alkylaminocarbonyl C₁-6 alkyl,
 5 wherein alkyl groups and aryl groups may be unsubstituted or
 substituted with one or more substituents selected from R¹ and R²; and

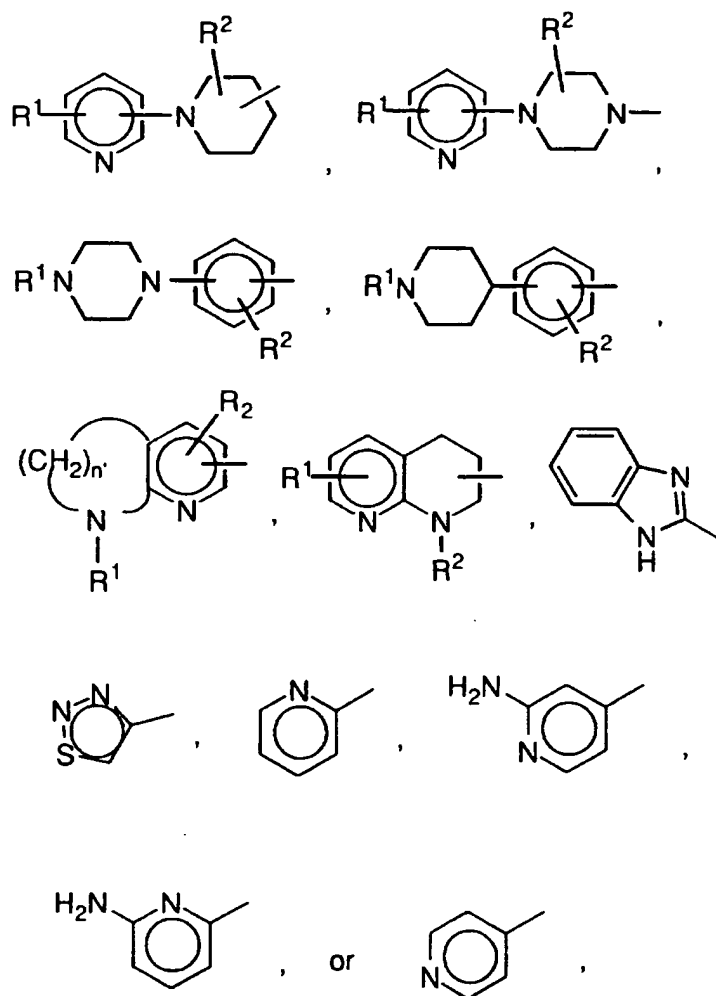
- R⁶ and R⁷ are independently
 hydrogen,
 10 C₁-8 alkyl,
 aryl C₁-8 alkyl,
 hydroxy,
 C₁-8 alkyloxy,
 aryl,
 15 aryl C₁-6 alkyloxy,
 C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 aryl C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 C₁-8 alkylaminocarbonylmethyleneoxy, or
 C₁-8 dialkylaminocarbonylmethyleneoxy,
 20 where m and n are integers 0-6.

In a subclass of the class of compounds described above are compounds of the formula



- 25 and pharmaceutically acceptable salts thereof, wherein
 X is

- 17 -



wherein n' is 2 or 3, and

wherein R^1 and R^2 are independently selected from the group consisting of

hydrogen, F, Cl, Br, I,

C₁-10 alkyl,

C₃-8 cycloalkyl,

aryl,

aryl C₁-8 alkyl,

amino,

amino C₁-8 alkyl,

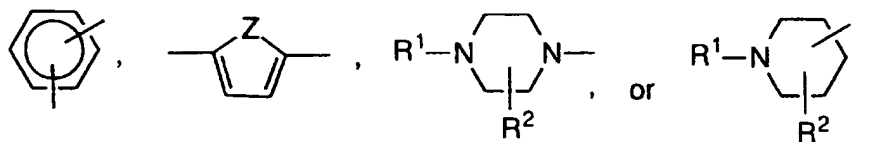
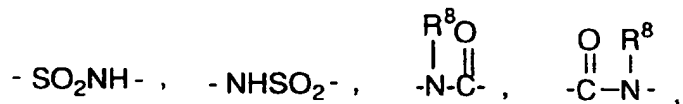
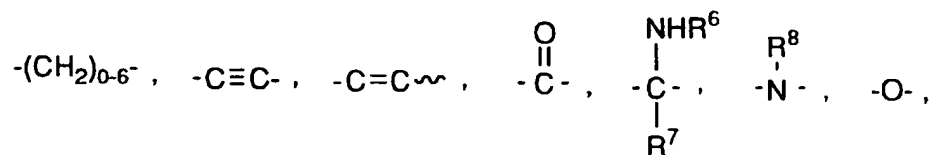
C₁-3 acylamino,

- 18 -

C₁-3 acylamino C₁-8 alkyl,
 C₁-6 alkylamino,
 C₁-6 alkylamino C₁-8 alkyl,
 C₁-6 dialkylamino,
 5 C₁-6 dialkylamino C₁-8 alkyl,
 C₁-4 alkoxy,
 C₁-4 alkoxy C₁-6 alkyl,
 carboxy,
 carboxy C₁-6 alkyl,
 10 C₁-3 alkoxycarbonyl,
 C₁-3 alkoxycarbonyl C₁-6 alkyl,
 carboxy C₁-6 alkyloxy and
 hydroxy,
 hydroxy C₁-6 alkyl;

15

Y is



where Z is O, NR⁸, or S; and R⁸ is defined as R¹ above;

- 19 -

R³ and R⁴ are independently

hydrogen,

a five or six membered mono or polycyclic aromatic ring system

containing 0, 1, 2, 3, or 4 heteroatoms selected from

nitrogen, oxygen and sulfur, either unsubstituted or

substituted, with one or more groups selected from

hydroxyl, halogen, cyano, trifluoromethyl, C₁₋₃ alkoxy,

C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxycarbonyl, C₁₋₅ alkyl,

aminoC₁₋₅ alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₅

alkyl, or hydroxycarbonylC₁₋₅ alkoxy,

-(CH₂)_n-aryl, wherein n=1-4 and aryl is defined as a five or six

membered mono or polycyclic aromatic ring system

containing 0, 1, 2, 3, or 4 heteroatoms selected from

nitrogen, oxygen and sulfur, either unsubstituted or

substituted, with one or more groups selected from

hydroxyl, halogen, cyano, trifluoromethyl, C₁₋₃ alkoxy,

C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxycarbonyl, C₁₋₅ alkyl,

aminoC₁₋₅ alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₅

alkyl, or hydroxycarbonylC₁₋₅ alkoxy,

halogen,

hydroxyl,

C₁₋₅alkylcarbonylamino,

arylC₁₋₅ alkoxy,

C₁₋₅ alkoxycarbonyl,

aminocarbonyl,

C₁₋₅ alkylaminocarbonyl,

C₁₋₅ alkylcarbonyloxy,

C₃₋₈ cycloalkyl,

oxo,

amino,

C₁₋₃ alkylamino,

aminoC₁₋₃ alkyl,

arylaminocarbonyl,

arylC₁₋₅alkylaminocarbonyl,

- 20 -

- aminocarbonyl-C₁₋₄ alkyl,
 hydroxycarbonyl,
 hydroxycarbonyl C₁₋₅ alkyl,
 C₁₋₆alkyl, either unsubstituted or substituted, with one or more
 5 groups selected from halogen, hydroxyl,
 C₁₋₅alkylcarbonylamino, arylC₁₋₅ alkoxy,
 C₁₋₅ alkoxycarbonyl, aminocarbonyl,
 C₁₋₅ alkylaminocarbonyl,
 C₁₋₅ alkylcarbonyloxy, C₃₋₈ cycloalkyl, oxo, amino,
 10 C₁₋₃ alkylamino, aminoC₁₋₃ alkyl,
 arylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl,
 aminocarbonyl-C₁₋₄ alkyl, hydroxycarbonyl, or
 hydroxycarbonyl C₁₋₅ alkyl, provided that the carbon atom
 to which R³ and R⁴ are attached bears only one
 15 heteroatom,
 -(CH₂)_m C≡CH,
 -(CH₂)_m C≡C-C₁₋₆ alkyl,
 -(CH₂)_m C≡C-C₃₋₇cycloalkyl,
 -(CH₂)_m C≡C- aryl,
 20 -(CH₂)_m C≡C-C₁₋₆ alkyl aryl,
 -(CH₂)_m CH=CH₂,
 -(CH₂)_m CH=CH C₁₋₆ alkyl,
 -(CH₂)_m CH=CH-C₃₋₇cycloalkyl,
 -(CH₂)_m CH=CH aryl,
 25 -(CH₂)_m CH=CH C₁₋₆ alkyl aryl,
 -(CH₂)_mSO₂C₁₋₆alkyl, or
 -(CH₂)_mSO₂C₁₋₆ alkylaryl;
- R⁵ is
 30 hydrogen,
 fluorine,
 C₁₋₈ alkyl,
 hydroxyl,
 hydroxy C₁₋₆ alkyl,

- 21 -

- carboxy,
carboxy C₁₋₆ alkyl,
C₁₋₆ alkyloxy.
C₃₋₈ cycloalkyl,
5 aryl C₁₋₆ alkyloxy,
aryl C₁₋₆ alkyl,
C₁₋₆ alkylcarbonyloxy,
amino C₁₋₆ alkyl,
amino,
10 C₁₋₆ alkylamino,
C₁₋₆ alkylamino C₁₋₆ alkyl,
aryl amino C₁₋₆ alkyl,
aryl amino,
aryl C₁₋₆ alkylamino,
15 aryl C₁₋₆ alkylamino C₁₋₆ alkyl,
aryl,
aryl C₁₋₆ alkylcarbonyloxy,
C₁₋₆ dialkylamino,
C₁₋₆ dialkylamino C₁₋₆ alkyl,
20 C₁₋₆ alkylaminocarbonyloxy,
C₁₋₈ alkylsulfonylamino,
C₁₋₈ alkylsulfonylamino C₁₋₆ alkyl,
aryl sulfonylamino C₁₋₆ alkyl,
aryl sulfonylamino,
25 aryl C₁₋₆ alkylsulfonylamino,
aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
C₁₋₈ alkyloxycarbonylamino,
C₁₋₈ alkyloxycarbonylamino C₁₋₈ alkyl,
aryl oxycarbonylamino C₁₋₈ alkyl,
30 aryl oxycarbonylamino,
aryl C₁₋₈ alkyloxycarbonylamino,
aryl C₁₋₈ alkyloxycarbonylamino C₁₋₈ alkyl,
C₁₋₈ alkylcarbonylamino,
C₁₋₈ alkylcarbonylamino C₁₋₆ alkyl,

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- aryl carbonylamino C₁-6 alkyl,
aryl carbonylamino,
aryl C₁-6 alkylcarbonylamino,
aryl C₁-6 alkylcarbonylamino C₁-6 alkyl,
5 aminocarbonylamino C₁-6 alkyl,
aminocarbonylamino,
C₁-8 alkylaminocarbonylamino,
C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
aryl aminocarbonylamino C₁-6 alkyl,
10 aryl aminocarbonylamino,
aryl C₁-8 alkylaminocarbonylamino,
aryl C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
aminosulfonylamino C₁-6 alkyl,
aminosulfonylamino,
15 C₁-8 alkylaminosulfonylamino,
C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino,
aryl C₁-8 alkylaminosulfonylamino,
20 aryl C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
C₁-6 alkylsulfonyl,
C₁-6 alkylsulfonyl C₁-6alkyl,
aryl sulfonyl C₁-6alkyl,
aryl sulfonyl,
25 aryl C₁-6 alkylsulfonyl,
aryl C₁-6 alkylsulfonyl C₁-6alkyl,
C₁-6 alkylcarbonyl,
C₁-6 alkylcarbonyl C₁-6 alkyl,
aryl carbonyl C₁-6alkyl,
30 aryl carbonyl,
aryl C₁-6 alkylcarbonyl,
aryl C₁-6 alkylcarbonyl C₁-6alkyl,
C₁-6 alkylthiocarbonylamino,
C₁-6 alkylthiocarbonylamino C₁-6 alkyl,

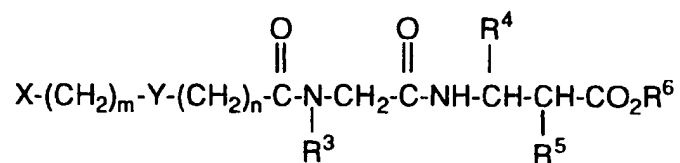
- 23 -

5 aryl thiocarbonylamino C₁₋₆ alkyl,
aryl thiocarbonylamino,
aryl C₁₋₆ alkylthiocarbonylamino,
aryl C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
aminocarbonyl C₁₋₆ alkyl,
aminocarbonyl,
C₁₋₈ alkylaminocarbonyl,
C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
10 aryl aminocarbonyl C₁₋₆ alkyl,
aryl aminocarbonyl,
aryl C₁₋₈ alkylaminocarbonyl, or
aryl C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
wherein alkyl groups and aryl groups may be unsubstituted or
substituted with one or more substituents selected from R¹ and R²; and
15 R⁶ and R⁷ are independently
hydrogen,
C₁₋₈ alkyl,
aryl,
20 aryl C₁₋₈ alkyl,
hydroxy,
C₁₋₈ alkyloxy,
aryl oxy,
aryl C₁₋₆ alkyloxy,
25 C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
C₁₋₈ alkylaminocarbonylmethyleneoxy, or
C₁₋₈ dialkylaminocarbonylmethyleneoxy,
where m and n are integers 0-6.

30

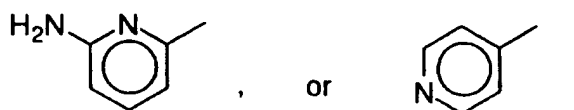
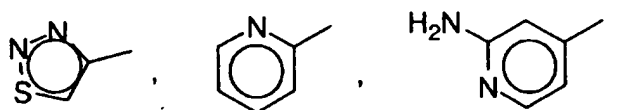
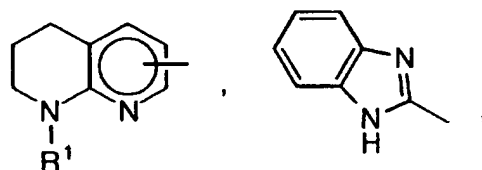
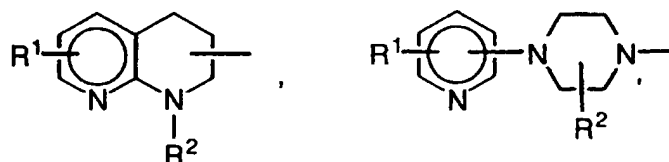
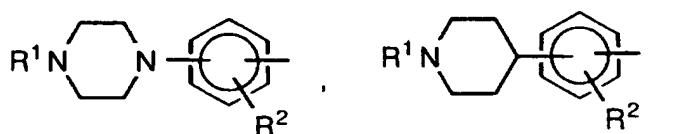
In a group of the subclass are compounds having the
formula

- 24 -



and pharmaceutically acceptable salts thereof, wherein

X is

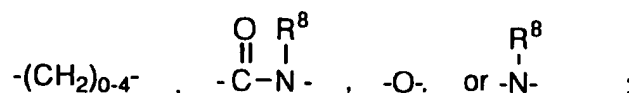


wherein R¹ and R² are independently selected from the group consisting of

hydrogen or
amino,
amino C₁-8 alkyl;

- 25 -

Y is

 R^8 is hydrogen or aryl C₀₋₈ alkyl; R^3 is

5 hydrogen,

a six membered monocyclic aromatic ring system, either
 unsubstituted or substituted, with one or more groups
 selected from hydroxyl, halogen, cyano, trifluoromethyl,
 C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxycarbonyl,
 10 C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl,
 hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅
 alkoxy,

-(CH₂)_n-aryl, wherein n=1-4 and aryl is defined as a six
 membered monocyclic aromatic ring system, either
 15 unsubstituted or substituted, with one or more groups
 selected from hydroxyl, halogen, cyano, trifluoromethyl,
 C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxycarbonyl,
 C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl,
 hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅
 20 alkoxy,

C₃₋₈ cycloalkyl, or

C₁₋₆alkyl, either unsubstituted or substituted, with C₃₋₈
 cycloalkyl;

 R^4 is

25 hydrogen,

-(CH₂)_n-aryl, wherein n=0-4 and aryl is defined as a six
 membered monocyclic aromatic ring system, either
 unsubstituted or substituted, with one or more groups
 selected from hydroxyl, halogen, cyano, trifluoromethyl,
 30 C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxycarbonyl,
 C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonylC₀₋₅ alkyl,
 or hydroxycarbonylC₁₋₅ alkoxy,

- 26 -

C₁₋₆alkyl, or
-(CH₂)₀₋₄ C≡CH;

R⁵ is

- 5 hydrogen,
 aryl sulfonylamino C₁₋₆ alkyl,
 aryl sulfonylamino,
 aryl C₁₋₆ alkylsulfonylamino,
 aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
10 C₁₋₈ alkylsulfonylamino,
 C₁₋₈ alkylsulfonylamino C₁₋₆ alkyl,
 aryl sulfonylamino C₁₋₆ alkyl,
 aryl sulfonylamino,
 aryl C₁₋₆ alkylsulfonylamino,
15 aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
 aminosulfonylamino C₁₋₆ alkyl,
 aminosulfonylamino,
 C₁₋₈ alkylaminosulfonylamino,
 C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
20 aryl aminosulfonylamino C₁₋₆ alkyl,
 aryl aminosulfonylamino,
 aryl C₁₋₈ alkylaminosulfonylamino,
 aryl C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
 C₁₋₆ alkylsulfonyl,
25 C₁₋₆ alkylsulfonyl C₁₋₆alkyl,
 aryl sulfonyl C₁₋₆alkyl,
 aryl sulfonyl,
 aryl C₁₋₆ alkylsulfonyl,
 aryl C₁₋₆ alkylsulfonyl C₁₋₆alkyl,
30

wherein alkyl groups and aryl groups may be unsubstituted or substituted with one or more substituents selected from R₁ and R₂;

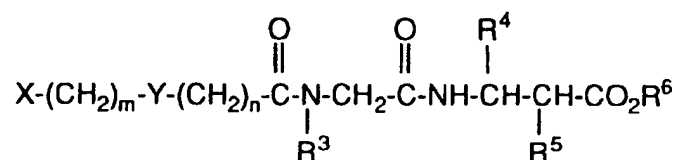
- 27 -

R⁶ is

hydrogen,
C₁-8 alkyl, or
aryl,
5 aryl C₁-8 alkyl;

m is an integer selected from 0 to 6; and
n is an integer selected from 0 to 6.

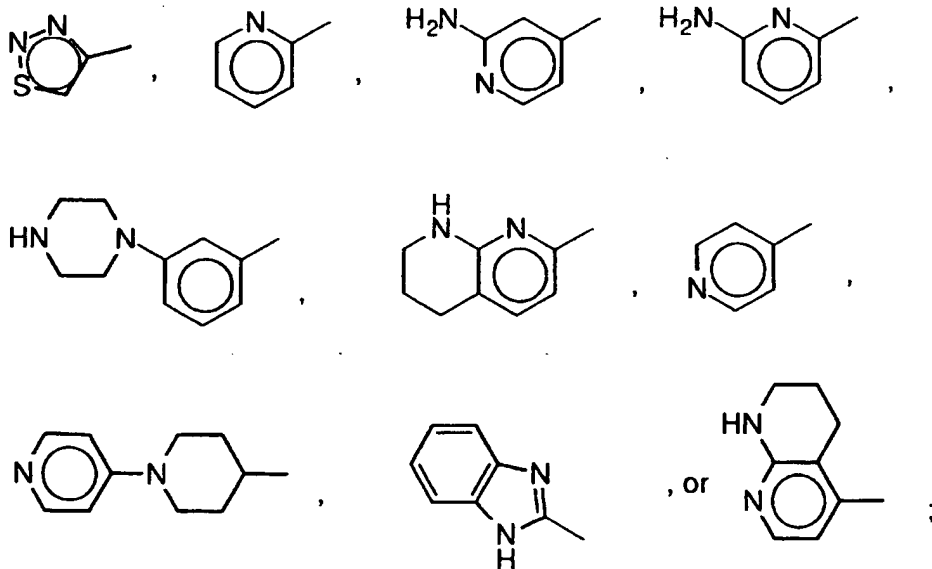
10 In a subgroup of the group are compounds having the
formula



and pharmaceutically acceptable salts thereof, wherein

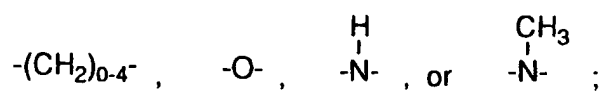
15

X is

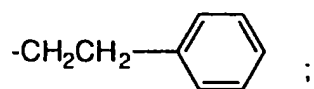


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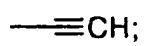
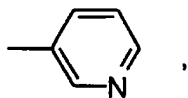
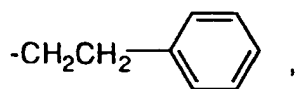
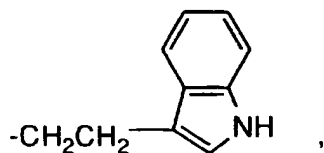
Y is

R³ is

5

hydrogen,
methyl,R⁴ is

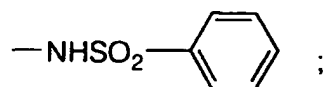
10

hydrogen,
methyl,

- 29 -

R⁵ is

hydrogen, or

5 R⁶ is

hydrogen,

methyl,

ethyl, or

t-butyl;

10

m is an integer selected from 0 to 6; and

n is an integer selected from 0 to 6.

Specific examples of this subgroup include

15 4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido-β-alanine t-butyl ester

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido-β-alanine

20

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)-β-alanine methyl ester

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)-β-alanine

25 trifluoroacetate salt

5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido-β-alanine ethyl ester

30 5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate salt

- 30 -

- 4-(2-Bocamino-pyridin-6-yl)butanoyl-sarcosine-3(R)-[(2-indol-3-yl)ethyl]- β -alanine ethyl ester
- 5 4-(2-Aminopyridin-6-yl)butanoyl-sarcosine-3(R)-[(2-indol-3-yl)ethyl]- β -alanine
- 4-(2-Boc-aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester
- 10 4-(2-Aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine
- 4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]- β -alanine ethyl ester
- 15 4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]- β -alanine
- 4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester
- 20 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester hydrochloride
- 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine
- 25 4-(2-Boc-amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine
- 30 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine
- 4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester

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4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester

5 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine

4-(Pyridin-4-yl)butanoyl-N-(2-phenylethyl)glycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester

10 4-(Pyridin-4-yl)butanoyl-N-(2-phenyl)glycyl-3(R)-(2-phenethyl)- β -alanine

4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine benzyl ester

15 4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine

20 4-(2-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine

4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine ethyl ester

25 4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine

3-[(N-Methyl)-N-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)- β -alanine ethyl ester

30 3-[(N-Methyl)-N-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)- β -alanine

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N-[N'-3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl]glycyl]-3(R)-methyl- β -alanine benzyl ester

5 N-[N'-[3-(1-Piperazinyl)benzoyl]glycyl]-3(R)-methyl- β -alanine trifluoroacetic acid salt

N-[N'-[3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl]glycyl]-3(R)-(2-phenethyl)- β -alanine methyl ester

10 N-[N'-[3-(1-Piperazinyl)benzoyl]glycyl]-3(R)-(2-phenethyl)- β -alanine trifluoroacetic acid salt

15 N-[N'-[3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl]-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)- β -alanine methyl ester

N-[N'-[3-(1-Piperazinyl)benzoyl]-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)- β -alanine trifluoroacetic acid salt

20 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanol-glycyl- β -alanine t-butyl ester

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl- β -alanine

25 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)-pyridin-3-yl- β -alanine ethyl ester

30 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)pyridin-3-yl- β -alanine

Ethyl N-pyridin-4-ylisonipecotyl-N-cyclopropylglycine-3(S)-ethynyl- β -alanine

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N-Pyridin-ylisonipecotyl-N-cyclopropylglycine-3(S)-ethynyl- β -alanine

5 Ethyl N-pyridin-4-ylnipecotyl-N-cyclopropylglycine-3(S)-ethynyl- β -alanine

N-Pyridin-4-ylnipecotyl-N-cyclopropylglycine-3(S)-ethynyl- β -alanine

10 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)gly-3(S)ethynyl- β -alanine ethyl ester

15 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)-ethynyl- β -alanine,

3-{2-[5-(1H-Benzoimidazol-2-yl-amino)-pentanoylamino]-acetylamino}-3(S)-pyridin-3-yl- propionic acid.

20 and pharmaceutically acceptable salts, such as the trifluoroacetate salt and the hydrochloric acid salt

25 Compounds of the invention are also useful for inhibiting the bone resorption activity of mammalian osteoclast cells by administering a pharmacologically effective amount of the compound to a patient in need of such activity to inhibit the activity of mammalian osteoclasts.

30 Compounds of the invention are also useful for inhibiting tumor growth in mammals. Pharmacologically effective amounts of the compounds, including pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit tumor growth. The growth of tumors depends on an adequate blood supply, which in turn depends on growth of new vessels into the tumor. New vessels are stimulated by factors secreted by the tumor. Inhibition of angiogenesis can cause tumor regression in animals.

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Compounds of the invention are also useful for treating and preventing diabetic retinopathy in mammals. Pharmacologically effective amounts of the compounds, including pharmaceutically acceptable salts thereof, are administered to the mammal, to inhibit
5 diabetic retinopathy.

Compounds are also useful in the prevention of restenosis of vessels.

The term "bone resorption activity" means the process by which osteoclasts solubilize bone minerals and increase the activity of
10 enzymes that degrade bone matrix.

Compounds of the invention are useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets. The above-mentioned compounds can be used in a method of acting upon a fibrinogen receptor which comprises
15 administering a therapeutically effective but non-toxic amount of such compound to a mammal, preferably a human. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and, dispersed therein, an effective but non-toxic amount of such compound is another feature of this invention.

20 The invention also includes the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the aggregation of blood platelets, preventing platelet thrombosis, preventing thromboembolism or preventing reocclusion, in a mammal.

25

DETAILED DESCRIPTION OF THE INVENTION

Fibrinogen receptor antagonist compounds of Formula I are useful in a method of inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood platelets.

30 Fibrinogen receptor antagonists of this invention are illustrated by compounds having the formula:

The following compounds were tested and found to inhibit platelet aggregation with IC₅₀ values between about 0.01 μ M and 100 μ M.

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4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester

5 4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)- β -alanine methyl ester

10 4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)- β -alanine trifluoroacetate salt

5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido- β -alanine ethyl ester

15 5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido- β -alanine trifluoroacetate salt

20 4-(2-Bocamino-pyridin-6-yl)butanoyl-sarcosine-3(R)-[(2-indol-3-yl)ethyl]- β -alanine ethyl ester

4-(2-Aminopyridin-6-yl)butanoyl-sarcosine-3(R)-[(2-indol-3-yl)ethyl]- β -alanine

25 4-(2-Boc-aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester

4-(2-Aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine

30 4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]- β -alanine ethyl ester

4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]- β -alanine

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- 4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester
- 5 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester hydrochloride
- 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine
- 10 4-(2-Boc-amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine
- 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine
- 15 4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester
- 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester
- 20 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine
- 25 4-(Pyridin-4-yl)butanoyl-N-(2-phenylethyl)glycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester
- 4-(Pyridin-4-yl)butanoyl-N-(2-phenyl)glycyl-3(R)-(2-phenethyl)- β -alanine
- 30 4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine benzyl ester

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4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine

5 4-(2-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine

4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine ethyl ester

10 4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine

15 3-[(N-Methyl)-N-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)- β -alanine ethyl ester

3-[(N-Methyl)-N-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)- β -alanine

20 N-[N'-3-(4-t-Butoxycarbonyl-1-piperiziny)benzoyl]glycyl}-3(R)-methyl- β -alanine benzyl ester

N-[N'-[3-(1-Piperaziny)benzoyl]glycyl]-3(R)-methyl- β -alanine trifluoroacetic acid salt

25 N-[N'-[3-(4-t-Butoxycarbonyl-1-piperaziny)benzoyl]glycyl]-3(R)-(2-phenethyl)- β -alanine methyl ester

N-[N'-[3-(1-Piperaziny)benzoyl]glycyl]-3(R)-(2-phenethyl)- β -alanine trifluoroacetic acid salt

30 N-[N'-[3-(4-t-Butoxycarbonyl-1-piperaziny)benzoyl]-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)- β -alanine methyl ester

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N-[N'-(3-(1-Piperazinyl)benzoyl)-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)- β -alanine trifluoroacetic acid salt

5 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanol-glycyl- β -alanine
t-butyl ester

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl- β -alanine

10 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)-pyridin-3-yl- β -alanine ethyl ester

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)pyridin-3-yl- β -alnine

15 Ethyl N-pyridin-4-ylisonipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine

20 N-Pyridin-ylisonipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine

Ethyl N-pyridin-4-ylnipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine

25 N-Pyridin-4-ylnipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)ethynyl- β -alanine ethyl ester

30 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)-ethynyl- β -alanine.

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One test which is used to evaluate fibrinogen receptor antagonist activity is based on evaluation of inhibition of ADP-stimulated platelets. Aggregation requires that fibrinogen bind to and occupy the platelet fibrinogen receptor site. Inhibitors of fibrinogen binding inhibit aggregation. In the ADP-stimulated platelet aggregation assay used to determine inhibition associated with the compounds claimed in the instant invention, human platelets are isolated from fresh blood, collected into acid citrate/dextrose by differential centrifugation followed by gel filtration on Sepharose 2B in divalent ion-free Tyrode's buffer (pH 7.4) containing 2% bovine serum albumin.

Platelet aggregation is measured at 37°C in a Chronolog aggregometer. The reaction mixture contains gel-filtered human platelets (2×10^8 per ml), fibrinogen (100 micrograms per ml (ug/ml)), Ca^{2+} (1 mM), and the compound to be tested. The aggregation is initiated by adding 10 mM ADP 1 minute after the other components are added. The reaction is then allowed to proceed for at least 2 minutes. The extent of inhibition of aggregation is expressed as the percentage of the rate of aggregation observed in the absence of inhibitor. The IC_{50} is the dose of a particular compound inhibiting aggregation by 50% relative to a control lacking the compound.

The term "pharmaceutically acceptable salts" shall mean non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid. Representative salts include the following salts:

acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, pamaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate,

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salicylate, stearate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, trifluoroacetate, and valerate.

Compounds of the present invention are chiral; included within the scope of the present invention are racemic mixtures and
5 separated enantiomers of the general formula. Furthermore, all diastereomers, including E, Z isomers, of the general formula are included in the present scope. Furthermore, hydrates as well as anhydrous compositions and polymorphs of the general formula are within the present invention.

10 Prodrugs, such as ester derivatives of described compounds, are compound derivatives which, when absorbed into the bloodstream of a warm-blooded animal, cleave in such a manner as to release the drug form and permit the drug to afford improved therapeutic efficacy.

15 The term "pharmaceutically effective amount" shall mean that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system or animal that is being sought by a researcher or clinician. The term "anti-coagulant" shall include heparin, and warfarin. The term "thrombolytic agent" shall
20 include agents such as streptokinase and tissue plasminogen activator. The term "platelet anti-aggregation agent" shall include agents such as aspirin and dipyridamole.

The term "alkyl" means straight or branched alkane containing 1 to about 10 carbon atoms, e.g., methyl, ethyl, n-propyl,
25 isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl radicals and the like, straight or branched alkene containing 2 to about 10 carbon atoms, e.g., propylenyl, buten-1-yl, isobutenyl, pentenylen-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, hepten-1-yl, and octen-1-yl radicals and the like, or straight or branched
30 alkyne containing 2 to about 10 carbon atoms, e.g., ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

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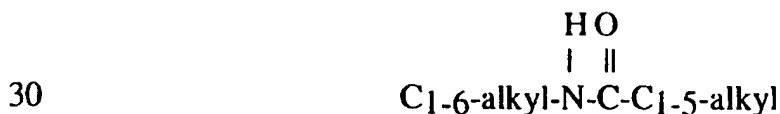
The term "aryl" means a 5- or 6-membered aromatic ring containing 0, 1, or 2 heteroatoms selected from O, N, and S. Examples of aryl include phenyl, pyridine, pyrimidine, imidazole, thiophene, oxazole, isoxazole, thiazole, and amino- and halogen- substituted derivatives thereof.

The terms "alkyloxy" or "alkoxy" include an alkyl portion where alkyl is as defined above. Examples of alkoxy include methyloxy, propyloxy, and butyloxy.

The terms "arylalkyl" and "alkylaryl" include an alkyl portion where alkyl is as defined above and to include an aryl portion where aryl is as defined above. The C_{0-n} or C_{1-n} designation where n may be an integer from 1-10 or 2-10 respectively refers to the alkyl component of the arylalkyl or alkylaryl unit. Examples of arylalkyl include benzyl, fluorobenzyl, chlorobenzyl, phenylethyl, phenylpropyl, fluorophenylethyl, chlorophenylethyl, thienylmethyl, thienylethyl, and thienylpropyl. Examples of alkylaryl include toluene, ethylbenzene, propylbenzene, methylpyridine, ethylpyridine, propylpyridine, butylpyridine, butenylpyridine, and pentenylpyridine.

The term "halogen" includes fluorine, chlorine, iodine and bromine.

The term "oxy" means an oxygen (O) atom. The term "thio" means a sulfur (S) atom. Under standard nomenclature used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. For example, a C₁₋₆ alkyl substituted with C₁₋₅ alkyl-carbonylamino is equivalent to



Compounds of the invention where X is a 5-membered monocyclic aromatic ring system, e.g., a thiazole system, can be prepared by forming an alkyl ester substituted derivative of the ring, e.g., methyl 4-(2-aminothiazol-4-yl)butanoate, forming the

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corresponding acid with HCl, and reacting with an amine to form the final product.

Compounds of the invention where X is a 6-membered monocyclic aromatic ring system, e.g., a pyridine system, can be prepared using 2-aminopyridine, 2-aminopicoline, 4-vinyl pyridine, etc., as described in Schemes 3, 4, and 10.

Compounds of the invention where X is a 9-membered polycyclic aromatic fused ring system can be prepared by reacting a substituted 5-membered ring starting material such as 2-amino-3-bromothiophene, 2-nitro-3-bromo thiophene, 2-amino-3-bromo pyrrole, and 2-amino-3-bromo furan, with an appropriate compound under suitable ring closure conditions to effect formation of the 9-membered fused ring system.

Compounds of the invention where X is a 10-membered polycyclic aromatic ring system can be prepared using a starting material such as naphthyridin (Hamada, Y. *et al.*, *Chem. Pharm. Bull. Soc.*, 1971, 19(9), 1857-1862), or by reacting an aminoaldehyde pyridine with a suitable ketone under suitable ring closure conditions to effect formation of the 10-membered fused ring system.

The examples illustrate procedures for preparing compounds of the invention where Y is $-(CH_2)_{0-4}$, $-O-$, and $-N(R^8)-$. To make compounds where Y is $-N(R^8)C(O)-$, an acid such as compound 1-4 can be subjected to a Curtius reaction to form the amine, and subsequent condensation to give the final product.

In the schemes and examples below, various reagent symbols have the following meanings:

BOC	
(or Boc):	t-butyloxycarbonyl
30 Pd-C:	Palladium on activated carbon catalyst
DMF:	Dimethylformamide
DMSO:	Dimethylsulfoxide
CBZ:	Carbobenzyloxy
CH ₂ Cl ₂ :	Methylene chloride

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- CHCl₃: chloroform
 EtOH: ethanol
 MeOH: methanol
 EtOAc: ethyl acetate
 5 HOAc: acetic acid
 BOP: Benzotriazol-1-yloxytris(dimethylamino)phosphonium,
 hexafluorophosphate
 EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
 hydrochloride
 10 Oxone: potassium peroxymonosulfate
 LDA: Lithium diisopropylamide
 PYCLU: Chloro-N,N,N',N'-bis(pentamethylene)formamidinium
 hexafluorophosphate

- 15 The compounds of the present invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion),
 20 intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an anti-aggregation agent.

- Compounds of the invention may be administered to
 25 patients where prevention of thrombosis by inhibiting binding of fibrinogen to the platelet membrane glycoprotein complex IIb/IIIa receptor is desired. They are useful in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular surgery where manipulation of arteries and organs, and/or the interaction of
 30 platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of this invention may be administered to these surgical patients to prevent the formation of thrombi and thromboemboli.

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Extracorporeal circulation is routinely used for cardiovascular surgery in order to oxygenate blood. Platelets adhere to surfaces of the extracorporeal circuit. Adhesion is dependent on the interaction between gp IIb/IIIa on the platelet membranes and
5 fibrinogen adsorbed to the surface of the circuit. (Gluszko *et al.*, *Amer. J. Physiol.*, 252(H), 615-621 (1987)). Platelets released from artificial surfaces show impaired hemostatic function. Compounds of the invention may be administered to prevent adhesion.

Other applications of these compounds include prevention
10 of platelet thrombosis, thromboembolism and reocclusion during and after thrombolytic therapy and prevention of platelet thrombosis, thromboembolism and reocclusion after angioplasty or coronary artery bypass procedures. They may also be used to prevent myocardial infarction.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound
15 or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the present invention, when used for the
25 indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 0.01-50 mg/kg/day and more preferably 0.01-20 mg/kg/day, e.g. 0.1 mg/kg/day, 1.0 mg/kg/day, 5.0 mg/kg/day, or 10 mg/kg/day.

Intravenously, the most preferred doses will range from about 1 to
30 about 10 mg/kg/minute during a constant rate infusion.

Advantageously, compounds of the present invention may be administered in divided doses of two, three, or four times daily. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal

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vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regime.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar

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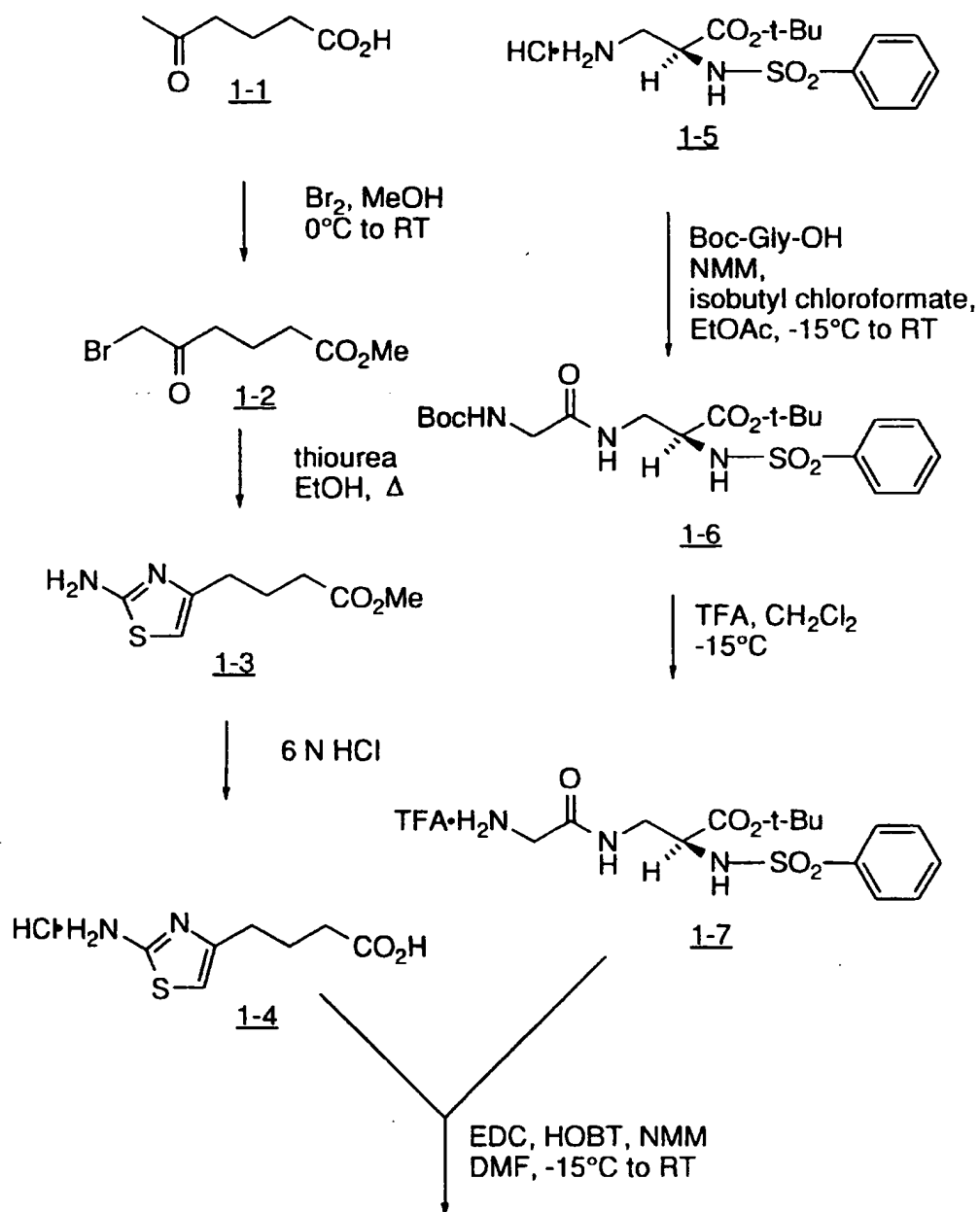
vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxy-ethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

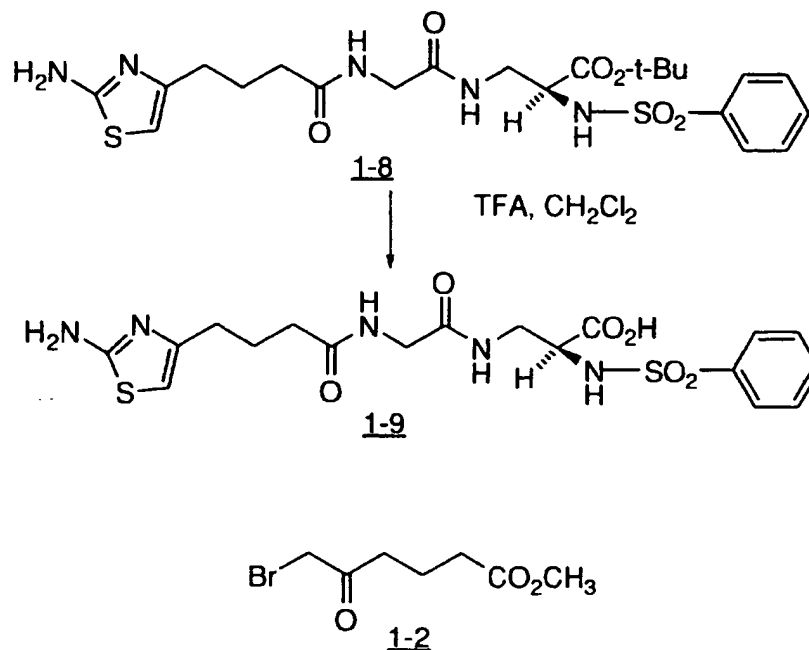
The compounds of the present invention can also be co-administered with suitable anticoagulation agents or thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies. They may also be combined with heparin, aspirin, or warfarin.

The novel compounds of the present invention were prepared according to the procedure of the following examples. The most preferred compounds of the invention are any or all of those specifically set forth in these examples. These compounds are not, however, to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. The following examples further illustrate details for the preparation of the compounds of the present invention. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. All temperatures are degrees Celsius unless otherwise noted.

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SCHEME 1

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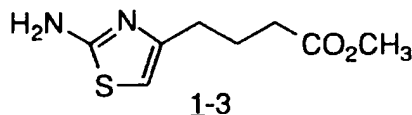
SCHEME 1 CONTINUED

5

Methyl 6-bromo-5-oxohexanoate (1-2)

- 5-Oxohexanoic acid (**1-1**, 5 mL, 42 mmol) was dissolved in 84 mL MeOH and cooled to 0°C. Br₂ (2.2 mL, 43 mmol) was added dropwise, and the reaction was stirred at RT overnight. After removing the MeOH by rotary evaporation, the residue was dissolved in ether, washed with water, sat. NaHCO₃ and brine, dried (Na₂SO₄), filtered and concentrated. Flash chromatography (silica, 10% EtOAc/hexane) provided the bromide-ester **1-2** as a yellow oil.
- TLC R_f 0.09 (silica, 15% EtOAc/hexane)
- ¹H-NMR (300 MHz, CDCl₃): δ 3.88 (s, 2H), 3.67 (s, 3H), 2.75 (t, J = 7 Hz, 2H), 2.37 (t, J = 7 Hz, 2H), 1.94 (qn, J = 7 Hz, 2H).

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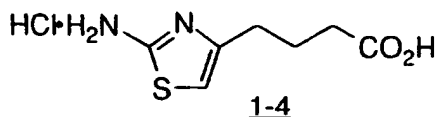


Methyl 4-(2-aminothiazol-4-yl)butanoate (1-3)

Bromide 1-2 (3.45 g, 15.5 mmol) and thiourea (1.4 g, 18 mmol) were combined in 77 mL EtOH and heated to reflux. After
 5 disappearance of 1-2, the EtOH was removed by rotary evaporation and the residue was diluted with EtOAc, washed with water and brine, then dried (MgSO₄), filtered and concentrated. The pH of the aqueous phase was adjusted to 7, and the solution was re-extracted with EtOAc (2x).
 These organic extracts were washed with brine, dried (MgSO₄), filtered
 10 and concentrated, combined with the first organic residues, then purified by flash chromatography (silica, EtOAc) providing aminothiazole 1-3 as a white solid.

TLC R_f 0.5 (silica, EtOAc)

¹H-NMR (400 MHz, CDCl₃): δ 6.09 (s, 1H), 5.19 (br s, 2H), 3.66 (s,
 15 3H), 2.55 (t, J = 7 Hz, 2H), 2.34 (t, J = 7 Hz, 2H), 1.96 (qn, J = 7 Hz, 2H).

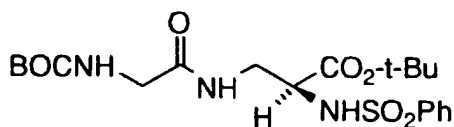


20 4-(2-Aminothiazol-4-yl)butanoic acid hydrochloride (1-4)

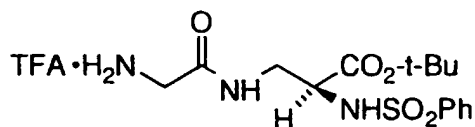
Ester 1-3 (1.3 g, 6.5 mmol) was dissolved in 32 mL 6 N HCl. After stirring overnight, the resulting suspension was concentrated, providing acid 1-4 as a white solid.

¹H-NMR (400 MHz, d₆-DMSO): δ 9.12 (br s, 1H), 6.51 (s, 1H), 3.50
 25 (br s), 2.51 (t, J = 7 Hz, 2H), 2.24 (t, J = 7 Hz, 2H), 1.77 (qn, J = 7 Hz, 2H).

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1-6N-Boc-glycyl-2(S)-phenylsulfonamido-β-alanine t-butyl ester (1-6)

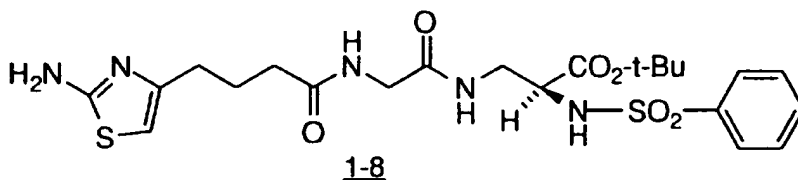
- N-Boc-glycine (255 mg, 1.5 mmol) was dissolved in 7.4 mL EtOAc, cooled to -15°C, then NMM (179 μL, 1.6 mmol) and isobutyl chloroformate (211 μL, 1.6 mmol) were added. After 20 min, amine 1-5 (500 mg, 1.5 mmol) and additional NMM (422 μL, 3.2 mmol) were added and the reaction was warmed to RT overnight. Following dilution with EtOAc, the mixture was washed with water, sat. NaHCO₃, 10% KHSO₄, and brine, dried (MgSO₄), filtered and concentrated, providing amide 1-6 as a white solid.
- TLC R_f 0.73 (silica, EtOAc)
- ¹H-NMR (300 MHz, CDCl₃): δ 7.84 (d, J = 7 Hz, 2H), 7.59 (ABX t, J = 7 Hz, 1H), 7.51 (ABX t, J = 7 Hz, 2H), 6.58 (br m, 1H), 5.58 (d, J = 8 Hz, 1H), 5.11 (br s, 1H), 3.90-3.78 (m, 3H), 3.72 (m, 1H), 3.40 (m, 1H), 1.48 (s, 9H), 1.28 (s, 9H).

1-7

- Glycyl-2(S)-phenylsulfonamido-β-alanine t-butyl ester trifluoroacetate salt (1-7)

- Protected amide 1-6 (576 mg, 1.26 mmol) was dissolved in 6.3 mL CH₂Cl₂, cooled to -15°C, and TFA (6.3 mL) was added. After 25 min the reaction was concentrated, providing amine 1-7. TLC R_f 0.36 (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc).

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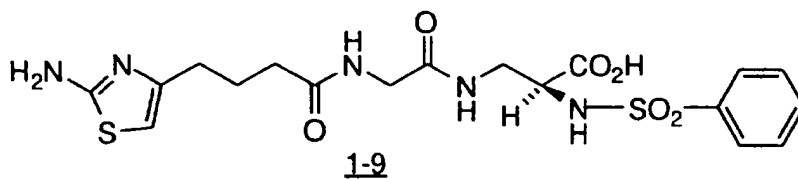


4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester (1-8)

Acid 1-4 (300 mg, 1.35 mmol), amine 1-7 (600 mg, 1.37 mmol), HOBT (219 mg, 1.14 mmol) and NMM (445 μ L, 4.04 mmol) were combined in 13 mL DMF, cooled to -15°C , and EDC (310 mg, 1.61 mmol) was added. The reaction was warmed to RT, stirred overnight, then diluted with EtOAc, washed with water, sat. NaHCO_3 , and brine, dried (MgSO_4), filtered and concentrated. Flash chromatography (silica, 20% MeOH/EtOAc) provided 1-8 as yellow solid.

TLC R_f 0.55 (silica, 20% MeOH/EtOAc)

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.80 (d, $J = 7$ Hz, 2H), 7.55 (ABX t, $J = 7$ Hz, 1H), 7.47 (ABX t, $J = 8$ Hz, 2H), 7.35 (br s, 1H), 7.04 (br m, 1H), 6.12 (s, 1H), 5.41 (br s, 2H), 4.05-3.95 (m, 3H), 3.69 (m, 1H), 3.39 (ddd, 1H), 2.70-2.55 (m, 2H), 2.33 (m, 2H), 2.01 (qn, $J = 7$ Hz, 2H), 1.27 (s, 9H).



4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine (1-9)

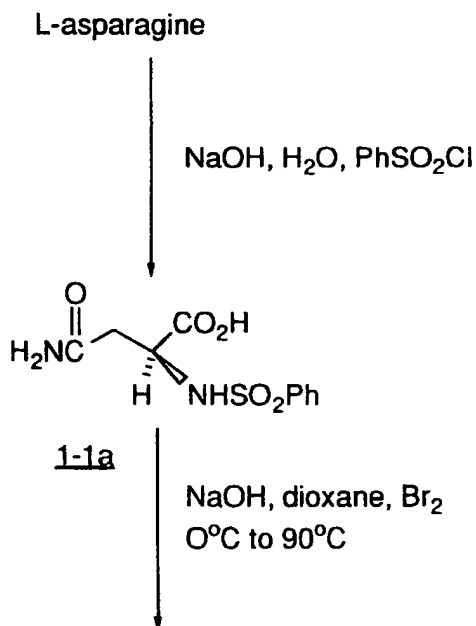
Ester 1-8 (365 mg, 0.69 mmol) was dissolved in CH_2Cl_2 (3.5 mL), then TFA (3.5 mL) was added. After 5 h the reaction mixture was concentrated, azeotroped with toluene, then purified by sequential flash chromatography (silica, 22:20:1:1

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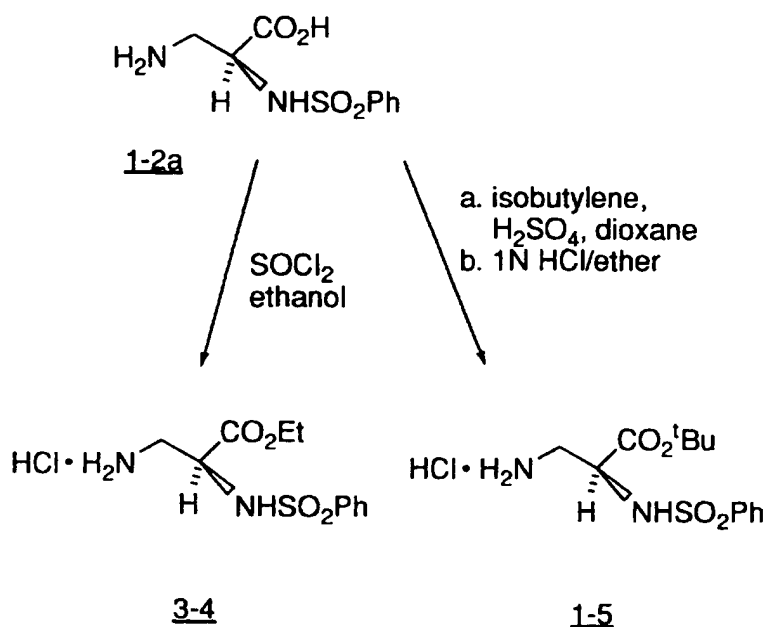
EtOAc/EtOH/H₂O/NH₄OH, then silica, 4:1:1 CH₂Cl₂/MeOH/HOAc, then 7:1:1 CH₂Cl₂/MeOH/HOAc), providing 1-9 as a white solid.

TLC R_f 0.33 (silica, 7:1:1 CH₂Cl₂/MeOH/HOAc)

¹H-NMR (400 MHz, CD₃OD): δ 7.86 (d, J = 7 Hz, 2H), 7.58 (ABX t, J = 7 Hz, 1H), 7.52 (ABX t, J = 8 Hz, 2H), 6.27 (s, 1H), 3.89 (AB d, J = 17 Hz, 1H), 3.77 (AB d, J = 17 Hz, 1H), 3.64 (t, J = 6 Hz, 1H), 3.53 (AB dd, 1H), 3.41 (AB dd, 1H), 2.57 (t, J = 7 Hz, 2H), 2.35-2.25 (m, 2H), 1.95 (m, 2H).

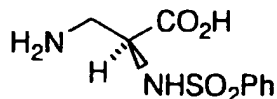


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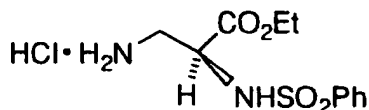
N-Phenylsulfonyl-L-asparagine (1-1a)

- To a stirred solution of L-asparagine (Aldrich) (10 g, 76 mmol), NaOH (3.4 g, 85 mmol), H₂O (50 mL), and dioxane (50 mL) at 0°C was added PhSO₂Cl (10.6 mL, 84 mmol). After 1 min, NaOH (3.4 g) in H₂O (50 mL) was added and the reaction mixture stirred for 30 min. The reaction mixture was then concentrated to remove the dioxane then washed with EtOAc. The aqueous phase was then cooled to 0°C and acidified to pH 5.0 with conc. HCl to effect product precipitation. The resulting solid was collected by filtration, washed with H₂O (20 mL) and dried at 50°C under vacuum to give N-phenylsulfonyl-L-asparagine (1-1a) as a white solid. R_f 0.40 (silica, 10:1:1 ethanol/H₂O/NH₄OH). ¹H NMR (300 MHz, D₂O) δ 7.59 (m, 2H), 7.26 (m, 3H), 3.92 (m, 1H), 3.02 (m, 1H), 2.35 (m, 1H).

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3-Amino-2(S)-phenylsulfonylaminopropionic acid (1-2b)

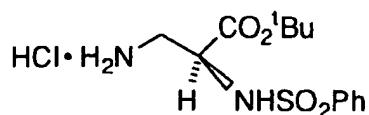
- To stirred solution of NaOH (15.6 g, 0.4 mol) in H₂O (70 mL), cooled with an icebath, was added bromine (3.6 mL, 0.07 mol) dropwise. After 5 min, a cold solution of N-phenylsulfonyl-L-asparagine, 1-1a (14.6 g, 54 mmol) and NaOH (4.3 g, 0.1 mol) in H₂O (50 mL) was added in one portion. The solution was stirred for 20 min at 0°C then 30 min at 90°C. The reaction mixture was recooled to 0°C, and the pH adjusted to 7 through dropwise addition of conc. HCl. The white precipitate formed was collected by filtration and then dried to give (1-2b) as a white solid. ¹H NMR (300 MHz, D₂O) δ 8.00, 7.50 (m, 5H), 3.88 (m, 1H), 3.37 (m, 1H), 3.12 (m, 1H).

3-4

- 15 Ethyl 3-Amino-2(S)-phenylsulfonylaminopropionate hydrochloride (3-4)

- Amino acid 1-2a (1.0 g, 4.1 mmol) was suspended in 20 mL EtOH, cooled to 0°C, and SOCl₂ (1.5 mL, 21 mmol) was added dropwise. After stirring at RT overnight the mixture was concentrated, trituated with Et₂O (2x), and dried, providing 3-4 (1.26 g) as a hygroscopic yellow solid.
- ¹H-NMR (300 MHz, d₆-DMSO): δ 8.30 (br s), 7.79 (d, J = 8 Hz, 2H), 7.70-7.60 (m, 3H), 4.21 (t, J Hz, 1H), 3.90-3.80 (m, 2H), 3.09 (ABX dd, J = 13, 6 Hz, 1H), 2.90 (ABX dd, J = 13, 8 Hz, 2H), 0.97 (t, J = 7 Hz, 3H).

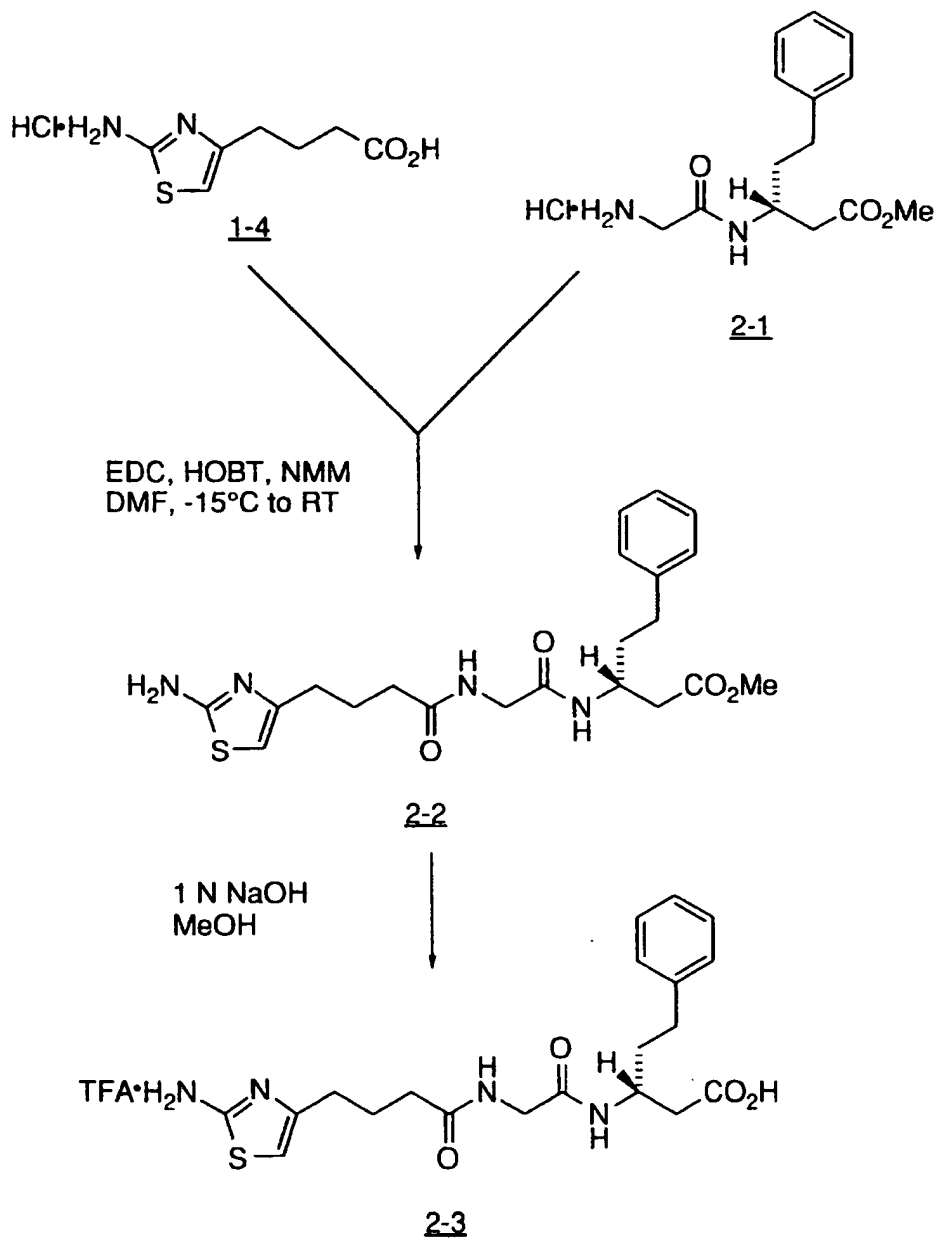
- 55 -

1-5

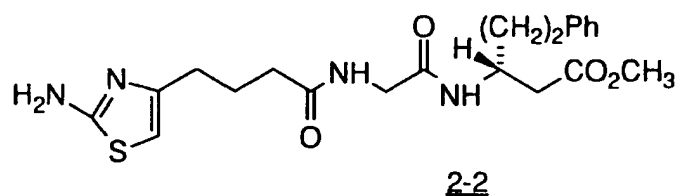
tert-Butyl 3-Amino-2(S)-phenylsulfonylamino-2-propionate hydro-chloride
(1-5)

- In a Fischer-Porter tube, a mixture of 1-2a (10.2 g, 42 mmol) and DME (150 mL) was sequentially treated with H_2SO_4 (6.4 mL, 0.12 mol), cooled to -78°C , and then condensed isobutylene (75 mL). The cooling bath was removed. After 24 h, ice/water (250 mL) was added followed by washing with ether (2x). The aqueous phase was basified with aq 6N NaOH, then saturated with NaCl, followed by extraction with EtOAc (3x). The combined extracts were washed with brine, dried (MgSO_4), and concentrated to give a white solid. This was dissolved in CH_2Cl_2 and treated with 1N HCl/ether (22 mL), and then concentrated to give 1-5 as a glassy yellow solid.
- ^1H NMR (400 MHz, DMSO) δ 8.25-8.00 (m, 4H), 7.85-7.58 (m, 5H), 4.08 (m, 1H), 3.10 (m, 1H), 2.73 (m, 1H), 1.17 (s, 9H).

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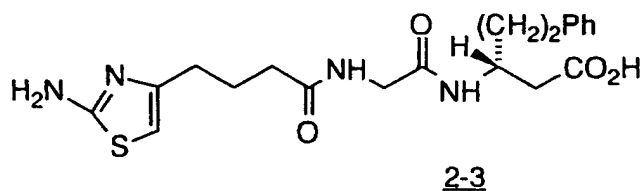
SCHEME 2

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4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)-β-alanine methyl ester (2-2)

- 5 Acid 1-4 (300 mg, 1.35 mmol), amine 2-1 (405 mg, 1.35 mmol) (prepared as described in Duggan *et al.*, U.S. Patent 5,264,420) HOBT (219 mg, 1.62 mmol) and NMM (445 μ L, 4.04 mmol) were combined in 7 mL DMF, cooled to -15°C , and EDC (310 mg, 1.61 mmol) was added. The reaction was warmed to RT, stirred overnight,
- 10 then diluted with EtOAc, washed with water, sat. NaHCO_3 , and brine, dried (MgSO_4), filtered and concentrated. Flash chromatography (silica, 10% MeOH/EtOAc) provided 2-2 as a yellow oil. TLC R_f 0.32 (silica, 10 % MeOH/EtOAc)
- 15 $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.82 (d, $J = 7$ Hz, 1H), 7.65 (d, $J = 8$ Hz, 1H), 7.40-7.10 (m, 5H), 6.93 (d, $J = 8$ Hz, 1H), 6.10 (s, 1H), 4.31 (m, 1H), 3.96 (ABX dd, $J = 17, 6$ Hz, 1H), 3.89 (ABX dd, $J = 17, 5$ Hz, 1H), 3.64 (s, 3H), 2.68-2.54 (m), 2.32-2.17 (m, 2H), 2.25-1.80 (m).



20

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)-β-alanine trifluoroacetate salt (2-3)

- 25 Ester 2-2 (220 mg, 0.51 mmol) and 1 N NaOH (1.3 mL, 1.3 mmol) were combined in 5 mL MeOH. After 3 d the reaction mixture was concentrated, purified by flash chromatography (silica, 9:1:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{HOAc}$), then preparative HPLC (C_{18} , 0.1 % TFA

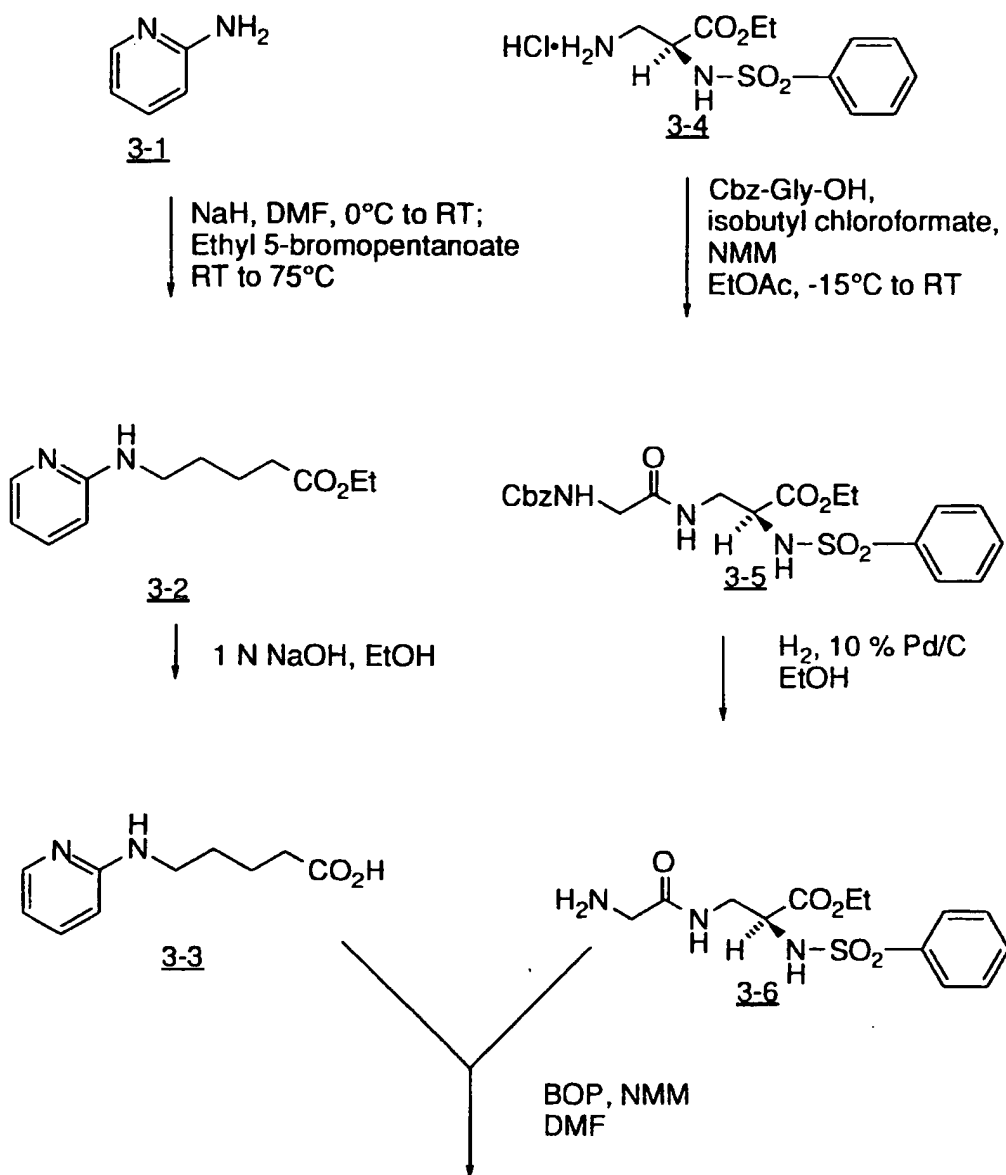
- 58 -

in CH₃CN/H₂O), providing, after lyophilization, acid 2-3 as a white solid.

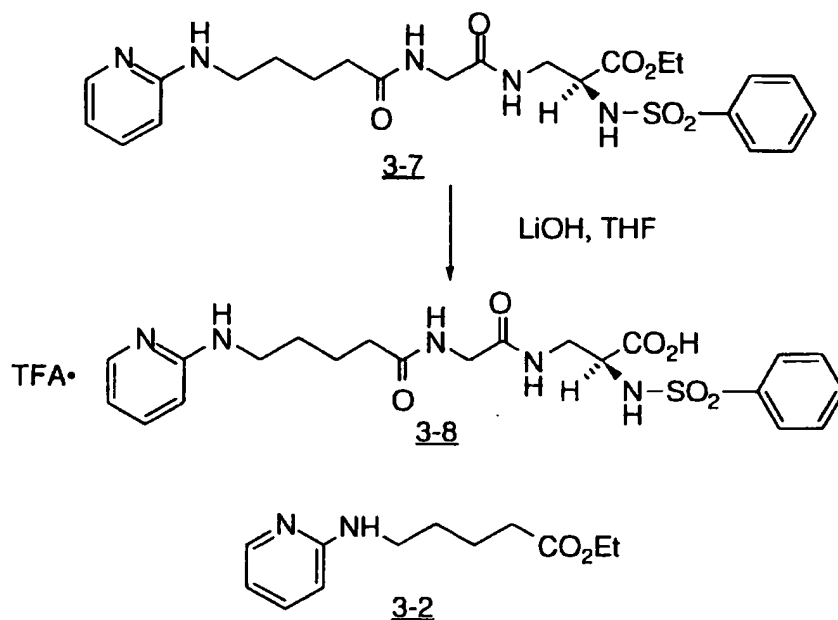
TLC R_f 0.54 (silica, 4:1:1 CH₂Cl₂/MeOH/HOAc)

¹H-NMR (400 MHz, CD₃OD): δ 7.26-7.10 (m, 5H), 6.52 (s, 1H), 4.23
5 (m, 1H), 3.88 (AB d, J = 17 Hz, 1H), 3.79 (AB d, J = 17 Hz, 1H), 2.72-
2.55 (m, 4H), 2.51 (d, J = 7 Hz, 2H), 2.34 (t, J = 7 Hz, 2H), 1.99-1.75
(m, 4H).

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SCHEME 3

- 60 -

SCHEME 3 CONTINUED

5

Ethyl 5-(2-pyridylamino)pentanoate (3-2)

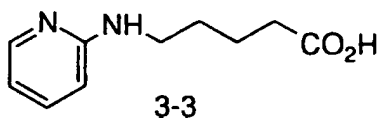
2-Aminopyridine (3-1, 1.97 g, 20.9 mmol) in 10 mL DMF was added to a suspension of NaH (60 % in oil, 1.00 g, 25 mmol) in 80 mL DMF cooled to 0°C. After warming to RT for 45 min, ethyl 5-bromopentanoate (4.2 mL, 25 mmol) was added dropwise. This mixture was heated at 75°C overnight, then cooled to RT, diluted with EtOAc, washed with water (2x), sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 50% then 70 % EtOAc/hexane) provided 3-2 as a yellow oil.

15 TLC R_f 0.55 (silica, 70 % EtOAc/hexane)

¹H-NMR (400 MHz, CDCl₃): δ 8.07 (dd, J = 5, 1 Hz, 1H), 7.40 (m, 1H), 6.55 (m, 1H), 6.37 (d, J = 8 Hz, 1H), 4.48 (br s, 1H), 4.13 (q, J = 7 Hz, 2H), 3.29 (q, J = 7 Hz, 2H), 2.35 (t, J = 7 Hz, 2H), 1.80-1.55 (m, 4H), 1.25 (t, J = 7 Hz, 3H).

20

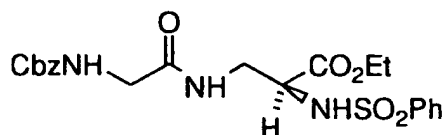
- 61 -

5-(2-Pyridylamino)pentanoic acid (3-3)

- Ester 3-2 (0.41 g, 1.84 mmol) was dissolved in 18 mL EtOH, 1 N NaOH (4.6 mL, 4.6 mmol) was added, and the reaction was stirred overnight. The pH of the solution was adjusted to 7 with 1 N HCl, and concentration provided a white solid containing acid 3-3 and NaCl.

TLC R_f 0.06 (silica, 19:1:1 CH₂Cl₂/MeOH/HOAc)

- ¹H-NMR (400 MHz, D₂O): δ 7.81 (m, 1H), 7.77 (d, J = 6 Hz, 1H), 6.96 (d, J = 9 Hz, 1H), 6.82 (t, J = 7 Hz, 1H), 3.36 (t, J = 7 Hz, 2H), 2.24 (m, 2H), 1.72-1.50(m, 4H).



15

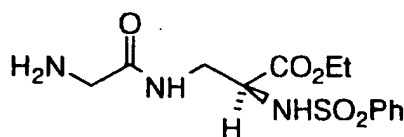
N-Cbz-glycyl-2(S)-phenylsulfonamido-β-alanine ethyl ester (3-5)

- N-Cbz-glycine (339 mg, 1.62 mmol) was dissolved in 8 mL EtOAc, cooled to -15°C, then NMM (196 μL, 1.8 mmol) and isobutyl chloroformate (230 μL, 1.8 mmol) were added. After 20 min, the mixed anhydride solution was added to amine 3-4 (0.50 mg, 1.6 mmol) suspended in 5 mL EtOAc and the reaction was warmed to RT for 90 min. Following dilution with EtOAc, the mixture was washed with water, sat. NaHCO₃, 5% KHSO₄, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 75 % EtOAc/hexane) provided amide 3-5 as a colorless oil.
- TLC R_f 0.29 (silica, 75 % EtOAc/hexane)

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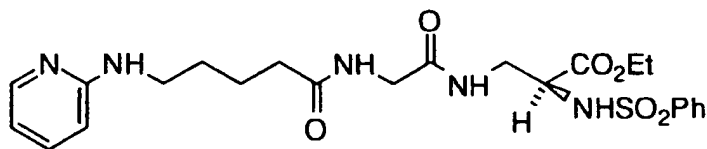
¹H-NMR (300 MHz, CDCl₃): δ 7.65-7.45 (m, 3H), 7.40-7.25 (m, 5H), 6.68 (t, J = 6 Hz, 1H), 5.83 (d, J = 8 Hz, 1H), 5.49 (t, J = 6 Hz, 1H), 5.15 (s, 2H), 4.04-3.95 (m, 3H), 3.89-3.85 (m, 2H), 3.73 (m, 1H), 3.46 (m, 1H), 1.11 (t, J = 7 Hz, 3H).

5

3-6

Glycyl-2(S)-phenylsulfonamido-β-alanine ethyl ester (3-6)

- Protected amine 3-5 (0.47 g, 1.01 mmol) was dissolved in 10 mL EtOH, 10 % Pd/C (94 mg) was added, and the reaction was stirred under an H₂ balloon. After 4 h, additional 10 % Pd/C was added (94 mg), and the reaction was continued for 3 d. The mixture was filtered through Celite, concentrated, and azeotroped with CHCl₃, providing amine 3-6 as a gum.
- ¹H-NMR (300 MHz, CDCl₃): δ 7.95 (m), 7.86 (d, J = 7 Hz, 2H), 7.60-7.45 (m, 3H), 4.05 (dd, J = 5, 6 Hz 1H), 3.96 (q, J = 7 Hz, 2H), 3.80-3.55 (m), 1.07 (t, J = 7 Hz, 3H).

3-7

20

5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido-β-alanine ethyl ester (3-7)

Acid 3-3 (186 mg, 0.55 mmol), amine 3-6 (150 mg, 0.46 mmol), NMM (0.20 mL, 1.8 mmol) and BOP (302 mg, 0.68 mmol)

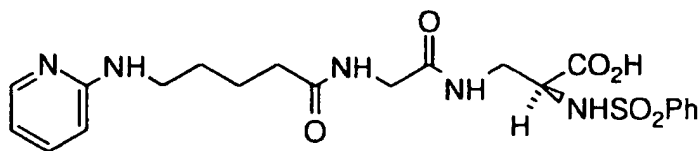
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were combined in 3 mL DMF. After 5 d the DMF was removed on a rotary evaporator, the residue was diluted with EtOAc, then washed with water, sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 25 % i-PrOH/EtOAc)

5 provided 3-7 as a colorless oil.

TLC R_f 0.30 (silica, 25 % i-PrOH/EtOAc)

¹H-NMR (400 MHz, CDCl₃): δ 8.05 (d, J = 4 Hz, 1H), 7.85 (d, J = 7 Hz, 2H), 7.57 (t, J = 7 Hz, 1H), 7.55-7.45 (m, 2H), 7.42 (m, 1H), 6.80 (br t, 1H), 6.54 (dd, J = 6, 4 Hz, 1H), 6.45 (m, 1H), 6.39 (d, J = 8 Hz, 1H), 5.19 (m, 1H), 4.16 (ABX dd, J = 17, 7 Hz, 1H), 4.08-3.95 (m), 3.85-3.75 (m, 2H), 3.29 (q, J = 6 Hz, 2H), 2.40-2.32 (m, 2H), 1.85 (m, J = 7 Hz, 2H), 1.75 (m, 2H), 1.10 (t, J = 7 Hz, 3H).



3-8

15

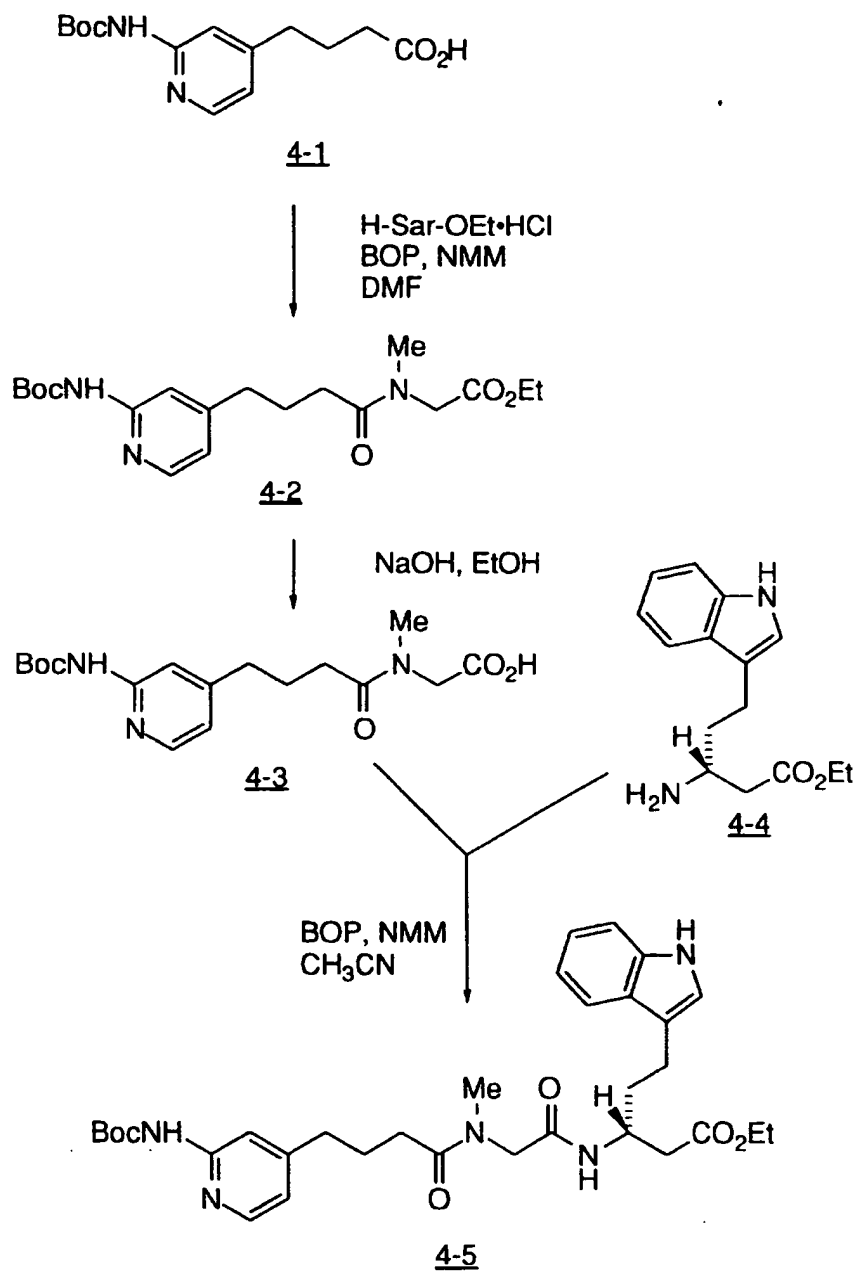
5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate salt (3-8)

Ester 3-7 (59 mg, 0.12 mmol) was dissolved in 1 mL THF, then 1 N LiOH (0.29 mL, 0.29 mmol) was added. After stirring overnight the reaction was concentrated, the mixture was concentrated. Flash chromatography (silica, 22:20:1:1 EtOAc/EtOH/H₂O/NH₄OH), followed by prep. HPLC (C-18, 0.1 % TFA/CH₃CN/H₂O) and lyophilization provided 3-8 as a white solid.

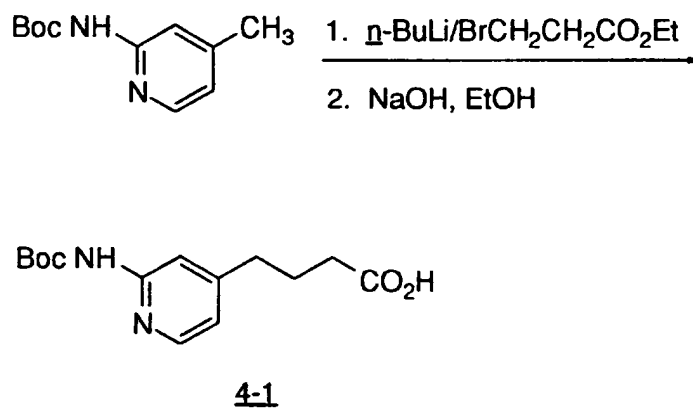
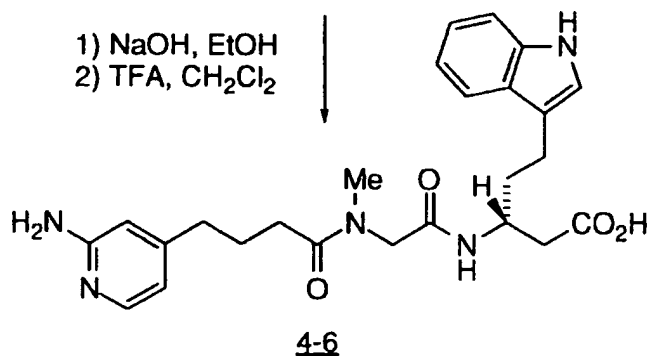
TLC R_f 0.26 (silica, 22:20:1:1 EtOAc/EtOH/H₂O/NH₄OH)

25 ¹H-NMR (400 MHz, D₂O): δ 7.83-7.75 (m, 3H), 7.70 (d, J = 6 Hz, 1H), 7.67 (d, J = 7 Hz, 1H), 7.58 (t, J = 7 Hz, 2H), 6.96 (d, J = 9 Hz, 1H), 6.80 (t, J = 7 Hz, 1H), 3.86-3.80 (m, 3H), 3.55 (dd, J = 14, 4 Hz, 1H), 3.36 (m, 2H), 3.29 (dd, J = 14, 8 Hz, 1H), 2.39 (m, 2H), 1.72 (m, 4H).

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SCHEME 4

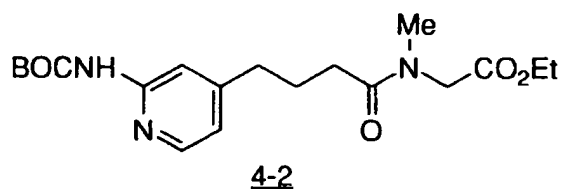
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SCHEME 4 CONTINUED4-(2-N-Boc-aminopyridin-4-yl)butanoic acid (4-1)

- The protected picoline (90 g, 0.43 mol) was dissolved in 3 L THF under N₂, cooled to -78°C, and n-BuLi (1.6 M, 675 mL, 1.08 mol) was added during 30 min. The mixture was allowed to warm to RT for 1 h, then the resulting orange suspension was cooled to -78°C. Methyl 3-bromopropionate (79 g, 0.47 mol) was added during 2 min. After 15 min the cooling bath was removed and the mixture was allowed to warm to -20°C at which point it was quenched with 60 mL HOAc in 250 mL THF. The solution was diluted with 2L EtOAc, washed with water, sat. NaHCO₃, and brine, dried (MgSO₄). The

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aqueous layers were re-extracted with EtOAc (2x), and these organic layers were filtered, concentrated, and dissolved in 1.5 L EtOH and 1.5 L 1 N NaOH (1.5 mol). After 1 h the reaction was concentrated by 1/3, diluted with 4 L EtOAc, the aqueous layer was removed. The pH of the aqueous layer was adjusted to 4-5 with 10% KHSO₄, then extracted with EtOAc (2 x 3L). The EtOAc layers were washed with brine, dried (MgSO₄), filtered and concentrated, providing 4-1 as a yellow oil.



10

4-(2-Boc-amino-pyridin-6-yl)butanoyl-sarcosine ethyl ester (4-2)

Acid 4-1 (200 mg, 0.71 mmol), H-Sar-OEt•HCl (130 mg, 0.84 mmol), NMM (314 μ L, 2.9 mmol) and BOP (378 mg, 0.86 mmol) were combined in 5 mL DMF. After stirring overnight the reaction mixture was diluted with EtOAc, washed with water (5x), sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 50-70 % EtOAc/hexane) provided 4-2 as a colorless oil.

15

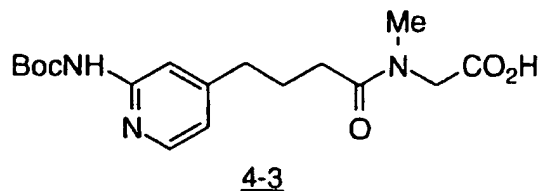
TLC R_f 0.54 (silica, 80% EtOAc/hexane)

20

¹H-NMR (400 MHz, CDCl₃): 4:1 mixture of amide rotomers, major rotomer δ 8.12 (d, J = 5 Hz, 1H), 7.79 (s, 1H), 7.48 (br s, 1H), 6.83 (d, J = 6 Hz, 1H), 4.19 (q, J = 7 Hz, 2H), 4.11 (s, 2H), 3.03 (s, 3H), 2.68 (t, J = 7 Hz, 2H), 2.39 (t, J = 7 Hz, 2H), 2.02 (qn, J = 7 Hz, 2H), 1.53 (s, 9H) 1.26 (t, J = 7 Hz, 3H).

25

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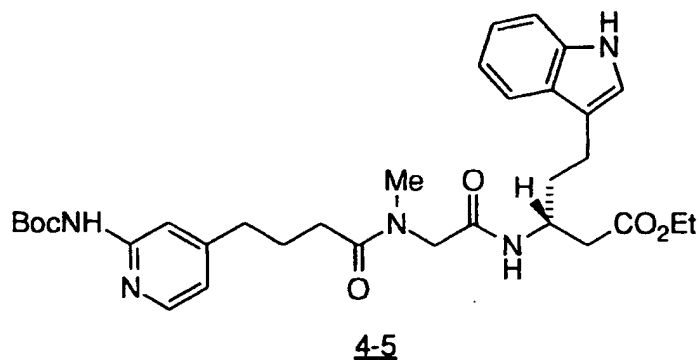


4-(2-Boc-amino-pyridin-4-yl)butanoyl-sarcosine (4-3)

Ester 4-2 (91 mg, 0.24 mmol) was dissolved in 2.4 mL EtOH, and 1 N NaOH (0.60 mL, 0.60 mmol) was added. After 45 min the mixture was concentrated, then diluted with EtOAc, washes with 10 % KHSO₄ and brine, dried (MgSO₄) filtered and re-concentrated, providing acid 4-3 as a glass.

TLC R_f 0.18 (silica, 18:1:1, CH₂Cl₂/MeOH/HOAc)

¹H-NMR (400 MHz, CDCl₃): 1:1 mixture of amide rotomers δ 8.03-7.82 (m, 3H), 6.86 (br s, 1H), 4.15/3.96 (s, 2H), 3.06/3.02 (s, 3H), 2.75-2.65 (m, 2H), 2.40 (m, 2H), 2.22-2.00 (m, 2H), 1.53 (s, 9H).



4-(2-Boc-amino-pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]-β-alanine ethyl ester (4-5)

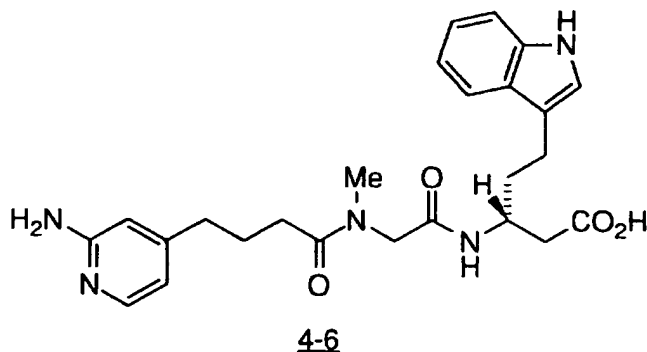
Acid 4-3 (84 mg, 0.24 mmol), amine 4-4 (see Duggan *et al.*, U.S. Patent 5,264,420) (68 mg, 0.26 mmol), NMM (104 μL, 0.95 mmol) and BOP (127 mg, 0.29 mmol) were combined in 2.4 mL CH₃CN. After stirring overnight the mixture was diluted with EtOAc, washed with water (4x), sat. NaHCO₃, and brine, dried (MgSO₄) and

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concentrated. Flash chromatography (silica, EtOAc) provided 4-5 as a colorless oil

TLC R_f 0.66 (silica, 20 % MeOH/EtOAc)

¹H-NMR (400 MHz, CDCl₃): 4:1 mixture of amide rotomers, major
5 rotomer δ 8.12 (s, 1H), 8.09 (d, J = 5 Hz, 1H), 7.78 (s, 1H), 7.55 (d, J = 8 Hz, 1H), 7.39 (s, 1H), 7.34 (d, J = 8 Hz, 1H), 7.17 (t, J = 8 Hz, 1H),
7.08 (t, J = 7 Hz, 1H), 7.03 (d, J = 2 Hz, 1H), 6.79 (dd, J = 5, 1 Hz, 1H),
6.71 (d, J = 9 Hz, 1H), 4.32 (m, 1H), 4.16-4.05 (m, 3H), 4.00 (AB d, J
10 = 15 Hz, 1H), 3.94 (AB d, J = 15 Hz, 1H), 3.04 (s, 3H), 2.77 (m, 2H),
2.63 (t, J = 8 Hz, 2H), 2.53 (m, 2H), 2.36 (m, 2H), 2.02-1.90 (m, 4H),
1.53 (s, 9H), 1.22 (t, J = 7 Hz, 3H).



15 4-(2-Aminopyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]-β-alanine (4-6)

Ester 4-5 (20 mg, 34 μmol) was dissolved in 350 μL EtOH, then 1 N NaOH (85 μL, 85 μmol) was added. After 2 h the reaction was diluted with EtOAc, washed with 10 % KHSO₄ and brine, dried (MgSO₄), filtered and concentrated. The residue was dissolved in 1 mL
20 CH₂Cl₂, treated with 1 mL TFA for 1 h, then concentrated and azeotroped with toluene. Flash chromatography (silica, 50:1:1, EtOH/H₂O/NH₄OH) provided 4-6 as an off-white solid.

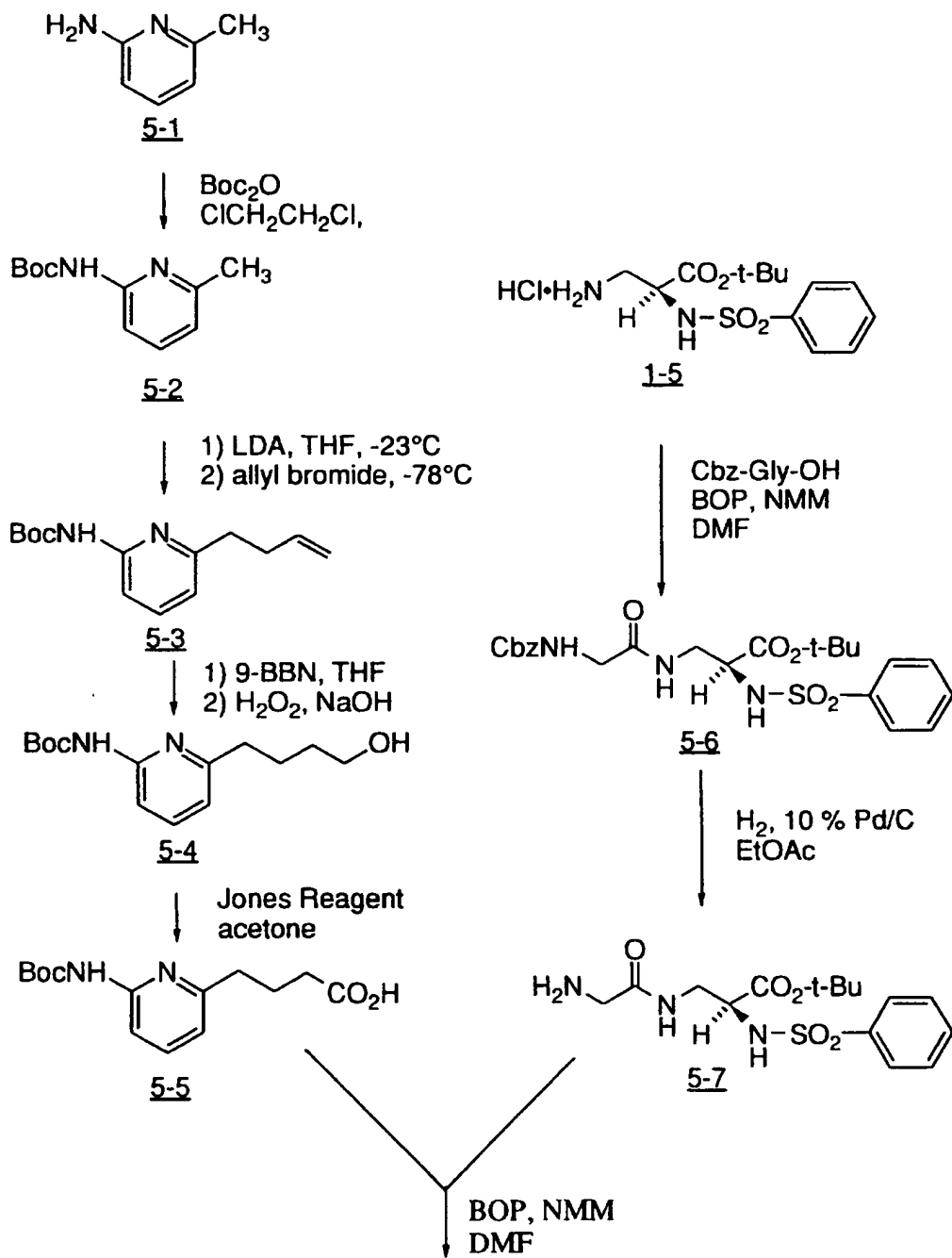
TLC R_f 0.55 (silica, 20:1:1 EtOH/H₂O/NH₄OH)

¹H-NMR (400 MHz, CD₃OD): 2:1 mixture of amide rotomers δ
25 7.72/7.67 (d, J = 6 Hz, 1H), 7.52 (t, J = 8 Hz, 1H), 7.30 (t, J = 8 Hz, 1H), 7.07-6.90 (m, 4H), 6.55/6.54 (s, 1H), 6.49 (s, 1H), 4.36-4.25 (m,

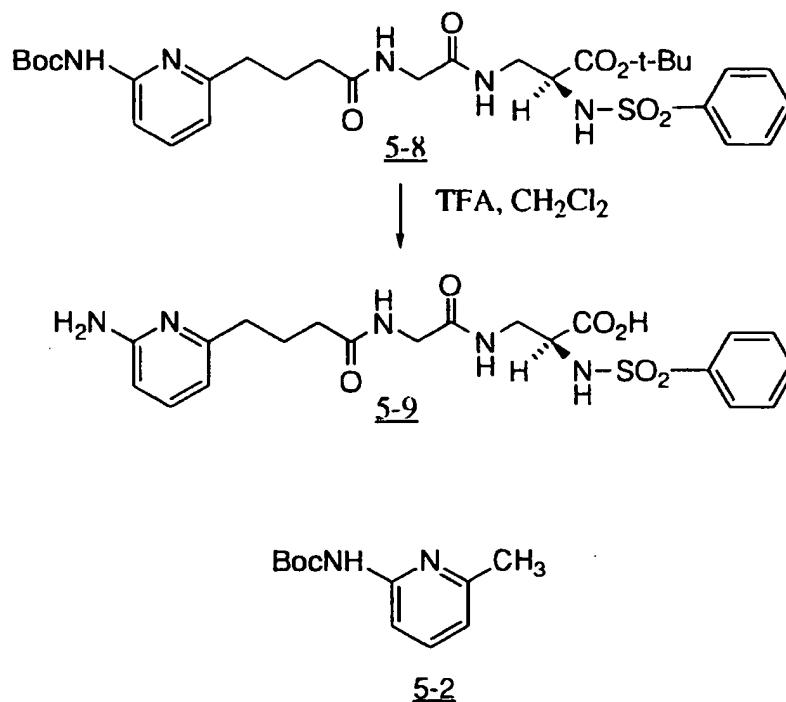
- 69 -

1H), 4.14-3.93 (m, 2H), 3.06/2.93 (s, 3H), 2.60 (t, J = 8 Hz, 2H), 2.55-2.45 (m, 4H), 2.34 (t, J = 7 Hz, 1H), 2.05-1.84 (m).

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SCHEME 5

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SCHEME 5 CONTINUED

5

2-(Boc-amino)-6-methylpyridine (5-2)

2-Amino-6-picoline (5.0 g, 46.2 mmol) and Boc₂O (11.1 g, 50.8 mmol) were combined in 150 mL dichloroethane. After heating at reflux for 6 h, additional Boc₂O (2.0 g, 9.2 mmol) was added, and the reaction was heated overnight. After concentration, the reaction mixture was flash filtered (silica, CH₂Cl₂), providing 5-2 as a waxy solid.

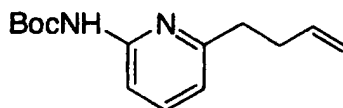
TLC R_f 0.21 (silica, CH₂Cl₂)

¹H-NMR (400 MHz, CDCl₃): δ 7.70 (d, J = 8 Hz, 1H), 7.54 (t, J = 8 Hz,

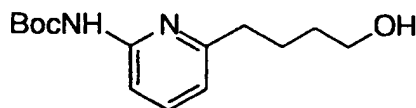
1H), 7.19 (br s, 1H), 6.80 (d, J = 7 Hz, 1H), 2.42 (s, 3H), 1.51 (s, 9H).

15

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5-32-(Boc-amino)-6-(4-butenyl)pyridine (5-3)

- Methylpyridine 5-2 (4.0 g, 19.2 mmol) was dissolved in 40 mL THF, cooled to -23°C, and LDA (2 M, 24 mL, 48 mmol) was added dropwise. After 30 min the mixture was cooled to -78°C and allyl bromide (2.49 mL, 2.88 mmol) was added dropwise. After 15 min more, the reaction was quenched with sat. NH₄Cl, warmed to RT, diluted with EtOAc, and the organic layer was washed with brine. After drying (MgSO₄), filtration and concentration, flash chromatography provided 5-3 as a yellow oil.
- TLC R_f 0.40 (silica, 75 % CH₂Cl₂/hexane)
- ¹H-NMR (300 MHz, CDCl₃): δ 7.72 (d, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.16 (br s, 1H), 6.80 (d, J = 7 Hz, 1H), 5.85 (m, 1H), 5.03 (dm, J = 17 Hz, 1H), 4.97 (dm, J = 10 Hz, 1H), 2.74 (t, J = 7 Hz, 2H), 2.42 (qm, J = 7 Hz, 2H), 1.52 (s, 9H).

5-42-(Boc-amino)-6-(4-hydroxybutyl)pyridine (5-4)

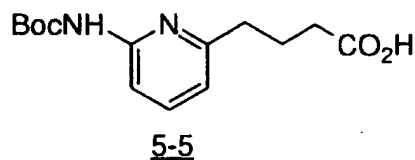
- A solution of alkene 5-3 (558 mg, 2.25 mmol) in 2 mL THF was added dropwise to a solution of 9-BBN (0.5 M in THF, 4.95 mL, 2.48 mmol). After stirring overnight, and additional portion of 9-BBN (0.5 M, 1.1 mL, 0.55 mmol) was added and the reaction was continued 1 h more. The reaction was quenched by the successive addition of EtOH (1.5 mL), 6 N NaOH (0.5 mL), and 30 % H₂O₂ (1.0 mL, exothermic), and heating to 50°C for 1h. The cooled mixture was saturated with K₂CO₃, then partitioned between EtOAc and water. The aqueous phase was reextracted with EtOAc, the combined organic

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phases were washed with brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 40 % EtOAc/hexane) provided alcohol 5-4 as a colorless oil.

TLC R_f 0.26 (silica, 40 % EtOAc/hexane)

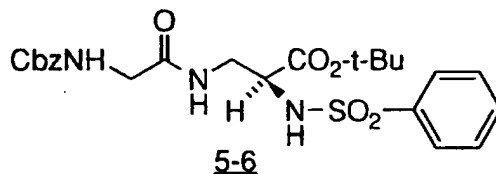
- 5 ¹H-NMR (400 MHz, CDCl₃): δ 7.73 (d, J = 8 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.20 (br s, 1H), 6.80 (d, J = 7 Hz, 1H), 3.67 (t, J = 7 Hz, 2H), 2.70 (t, J = 7 Hz, 2H), 1.77 (qn, J = 7 Hz, 2H), 1.61 (m, 2H), 1.51 (s, 9H).



10 4-(2-Boc-aminopyridin-6-yl)butanoic acid (5-5)

A solution of alcohol 5-4 (247 mg, 0.93 mmol) in 5 mL acetone was cooled to 0°C and a solution of Jones Reagent was added dropwise. As the color of the reaction changed from brown to green, additional Jones Reagent was added, until the alcohol was no longer detected by TLC (3.5 h). After quenching with i-PrOH the mixture was diluted with EtOAc, washed with 5 % KHSO₄ and brine, dried (MgSO₄), filtered and concentrated, providing 5-5 as an off-white waxy solid.

- 15 ¹H-NMR (400 MHz, CDCl₃): δ 9.13 (br s, 1H), 7.90 (d, J = 8 Hz, 1H),
 20 7.64 (t, J = 8 Hz, 1H), 6.85 (d, J = 8 Hz, 1H), 2.80 (t, J = 8 Hz, 2H),
 2.46 (t, J = 7 Hz, 2H), 2.01 (qn, J = 7 Hz, 2H), 1.54 (s, 9H).



N-Cbz-glycyl-2(S)-phenylsulfonamido-beta-alanine t-butyl ester (5-6)

- 25 Amine 1-5 (0.42 g, 1.25 mmol), Cbz-Gly-OH (288 mg, 1.38 mmol), NMM (0.55 mL, 5.0 mmol) and BOP (829 mg, 1.88

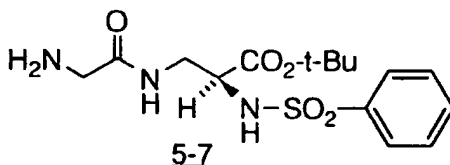
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mmol) were combined in 6 mL DMF. After stirring overnight the solvent was evaporated, the residue was taken up in EtOAc, the organic solution was washed with water (2x), 5 % KHSO₄, sat. NaHCO₃ and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography

5 (silica, 60 % EtOAc/hexane) provided 5-6 as a white glass.

TLC R_f 0.27 (silica, 60 % EtOAc/hexane)

¹H-NMR (400 MHz, CDCl₃): δ 7.83 (d, J = 7 Hz, 2H), 7.58 (t, J = 7 Hz, 1H), 7.50 (t, J = 8 Hz, 2H), 7.42-7.30 (m, 5H), 6.55 (br s, 1H), 5.59 (d, J = 7 Hz, 1H), 5.40 (br s, 1H), 5.16 (s, 2H), 3.95-3.70 (m, 4H), 3.34 (m, 10 1H), 1.27 (s, 9H).

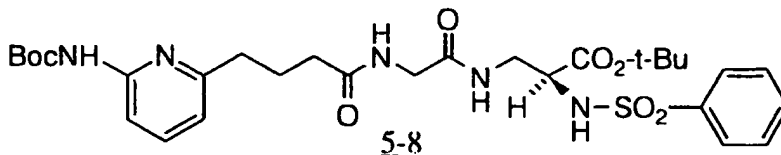


Glycyl-2(S)-phenylsulfonamido-β-alanine t-butyl ester (5-7)

15 A solution of 5-6 (0.54 g, 1.10 mmol) in 11 mL EtOAc was treated with 10 % Pd/C (108 mg) and stirred under a H₂ balloon overnight. After addition of more 10% Pd/C (100 mg) and hydrogenation for 5 d the mixture was filtered through Celite and concentrated, providing 5-6 as a white glass.

20 ¹H-NMR (400 MHz, CD₃OD): δ 7.84 (dm, J = 8 Hz, 2H), 7.61 (tm, J = 8 Hz, 1H), 7.54 (tm, J = 8 Hz, 2H), 4.00 (dd, J = 8, 5 Hz, 1H), 3.59 (dd, J = 14, 5 Hz, 1H), 3.37 (s, 2H), 1.25 (s, 9H).

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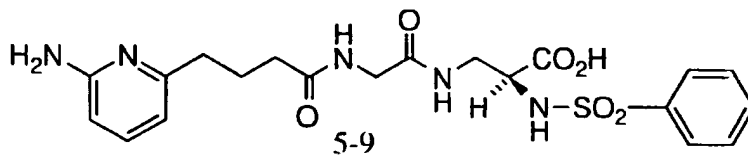


4-(2-Boc-aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester (5-8)

- 5 Acid 5-5 (144 mg, 0.51 mmol), amine 5-7 (202 mg, 0.56 mmol), NMM (226 μ L, 2.1 mmol) and BOP (241 mg, 0.77 mmol) were combined in 2.6 mL DMF. After stirring overnight the solvent was evaporated, the residue was dissolved in EtOAc, washed with water, sat. NaHCO₃, 5 % KHSO₄, and brine, dried (MgSO₄), filtered and
- 10 concentrated. Flash chromatography (silica, 10 % CHCl₃/EtOAc) provided 5-8 as an off-white glass.

TLC R_f 0.22 (silica, 10 % CHCl₃/EtOAc)

- ¹H-NMR (400 MHz, d₆-DMSO): δ 9.53 (s, 1H), 8.23 (br d, J = 7 Hz, 1H), 7.98 (t, J = 6 Hz, 1H), 7.91 (t, J = 6 Hz, 1H), 7.76 (d, J = 7 Hz, 2H), 7.65-7.53 (m, 5H), 6.87 (d, J = 7 Hz, 1H), 3.85 (br s, 1H), 3.60 (t, J = 5 Hz, 2H), 3.20-3.10 (m, 2H), 2.60 (t, J = 7 Hz, 2H), 2.15 (t, J = 7 Hz, 2H), 1.85 (qn, J = 7 Hz, 2H), 1.46 (s, 9H), 1.18 (s, 9H).



- 20 4-(2-Aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine (5-9)

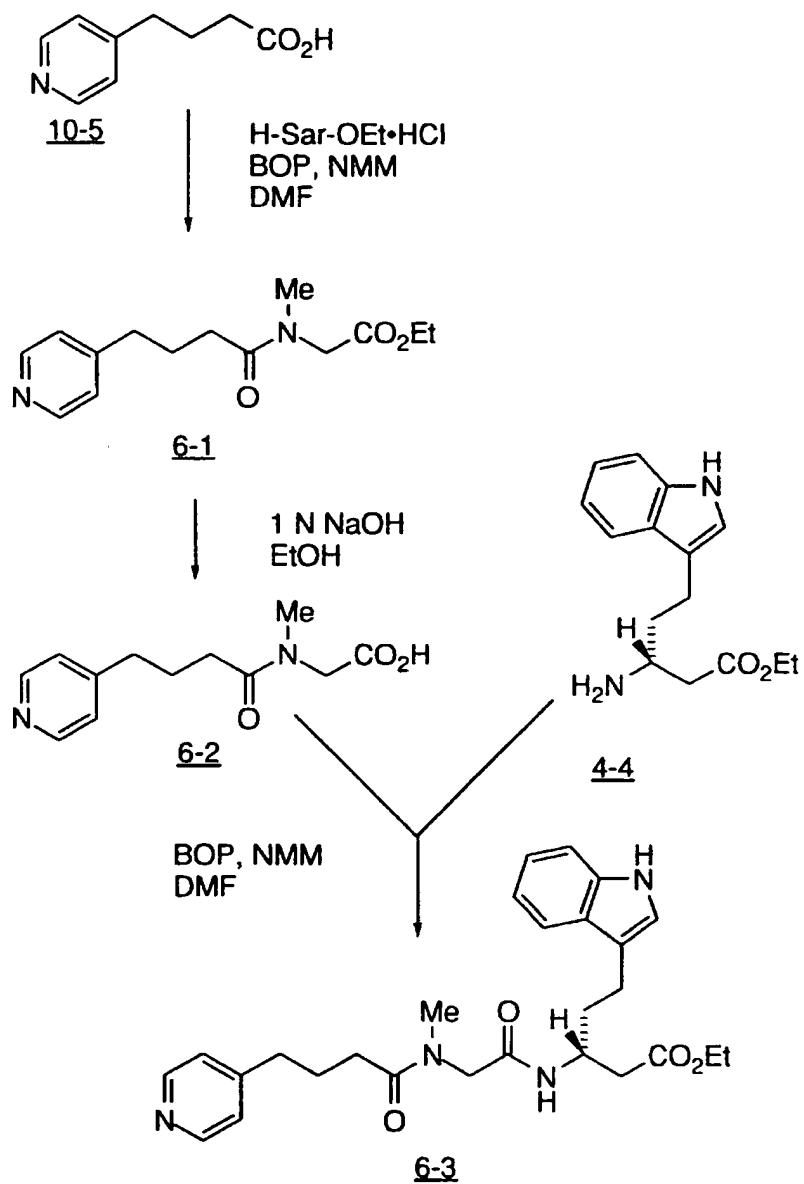
- A solution of 5-8 (138 mg, 0.22 mmol) in 1 mL CH₂Cl₂ was cooled to 0°C, treated with 1 mL TFA, and warmed to RT for 5 h. After concentration and azeotrope with toluene the residue was
- 25 purified by flash chromatography (silica, 12:20:1:1, EtOAc/EtOH/H₂O/NH₄OH), providing 5-9 as a colorless glass.

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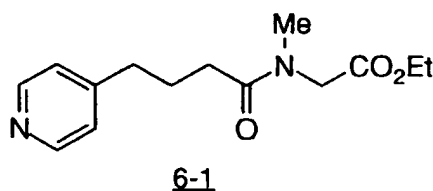
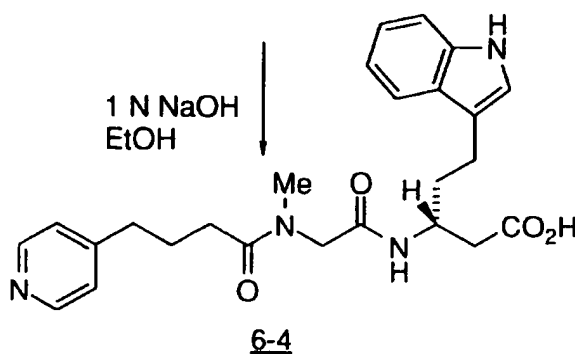
TLC R_f 0.34 (silica, 12:20:1:1, EtOAc/EtOH/H₂O/NH₄OH)

¹H-NMR (400 MHz, D₂O): δ 7.76 (dm, J = 7 Hz, 2H), 7.55-7.48 (m, 4H), 6.69 (d, J = 7 Hz, 1H), 6.57 (d, J = 8 Hz, 1H), 3.72-3.62 (m, 2H), 3.55 (dd, J = 8, 5 Hz, 1H), 3.37 (dd, J = 13, 8 Hz, 1H), 3.13 (dd, J = 13, 8 Hz, 1H), 2.63 (t, J = 7 Hz, 2H), 2.34 (t, J = 7 Hz, 2H), 1.96 (qn, J = 7 Hz, 2H).

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SCHEME 6

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SCHEME 6 CONTINUED

5

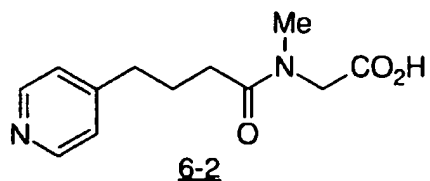
4-(Pyridin-4-yl)butanoyl-sarcosine ethyl ester (6-1)

4-(4-Pyridyl)butanoic acid 10-5 (100 mg, 1.8 mmol), H-Sar-OEt·HCl (300 mg, 2.0 mmol), BOP (965 mg, 2.2 mmol) and NMM (700 μ L, 6.4 mmol) were combined in 9 mL DMF. After stirring overnight the mixture was diluted with EtOAc, washed with water (4x), sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 80% to 100 % EtOAc/hexane) provided 6-1 as a colorless oil.

TLC R_f 0.44 (silica, 20 % MeOH/EtOAc)

¹H-NMR (400 MHz, CDCl₃): 4:1 mixture of amide rotomers, major rotomer δ 8.50 (d, J = 5 Hz, 2H), 7.14 (d, J = 5 Hz, 2H), 4.20 (q, J = 7 Hz, 2H), 4.12 (s, 2H), 3.03 (s, 3H), 2.70 (t, J = 8 Hz, 2H), 2.39 (t, J = 7 Hz, 2H), 2.02 (qn, J = 7 Hz, 2H), 1.23 (t, J = 7 Hz, 3H).

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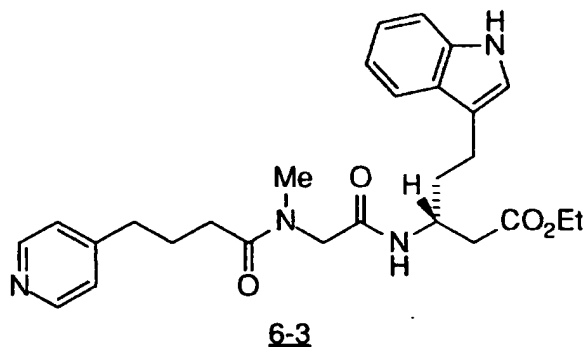
4-(Pyridin-4-yl)butanoyl-sarcosine (6-2)

Ester 6-1 (324 mg, 1.22 mmol) was dissolved in 6 mL EtOH, then 1 N NaOH (2.4 mL, 2.4 mmol) was added. After stirring overnight the mixture was concentrated, rediluted with EtOAc, extracted into 10 % KHSO₄, then concentrated, providing acid 6-2, along with inorganic salts.

TLC R_f 0.16 (silica, 4:1:1 CH₂Cl₂/MeOH/HOAc)

¹H-NMR (400 MHz, CD₃OD): 1:1 mixture of amide rotomers, δ 8.41

(br s, 2H), 7.33 (m, 2H), 4.00/3.90 (s, 2H), 3.05/2.95 (s, 3H), 2.77-2.67 (m, 2H), 2.48/2.37 (t, J = 7 Hz, 2H), 2.00-1.90 (m, 2H).

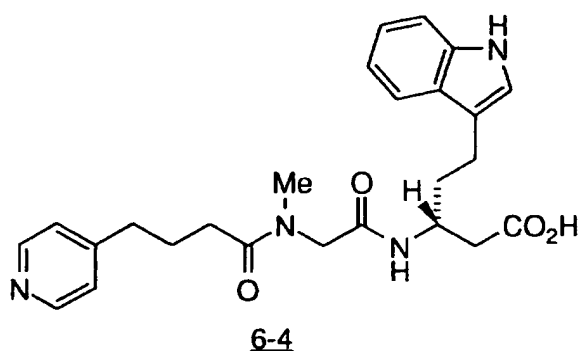


4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]-β-alanine ethyl ester (6-3)

Acid 6-2 (288 mg, 1.22 mmol), amine 4-4 (318 mg, 1.22 mmol), BOP (647 mg, 1.5 mmol), and NMM (462 μL, 4.2 mmol) were combined in 6 mL DMF. After stirring overnight the mixture was diluted with EtOAc, washed with water (4x), sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, EtOAc then 5 % MeOH/EtOAc) provided 6-3 as an orange oil. TLC R_f 0.4 (20 % MeOH/EtOAc)

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¹H-NMR (400 MHz, CDCl₃): 4:1 mixture of amide rotomers, major rotomer δ 8.47 (br d, J = 5 Hz, 2H), 8.02 (br d, J = 6 Hz, 2H), 7.58 (dd, J = 16, 8 Hz, 1H), 7.34 (dd, J = 8, 4 Hz, 1H), 7.20-7.03 (m, 3H), 7.01 (s, 1H), 6.72 (d, J = 9 Hz, 1H), 4.33 (m, 1H), 4.1 (t, J = 7 Hz, 3H), 3.98 (s, 2H), 3.05 (s, 3H), 2.90-2.45 (m), 2.39 (t, J = 7 Hz, 2H), 2.02-1.70 (m), 1.23 (t, J = 7 Hz, 3H).



10 4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]-β-alanine (6-4)

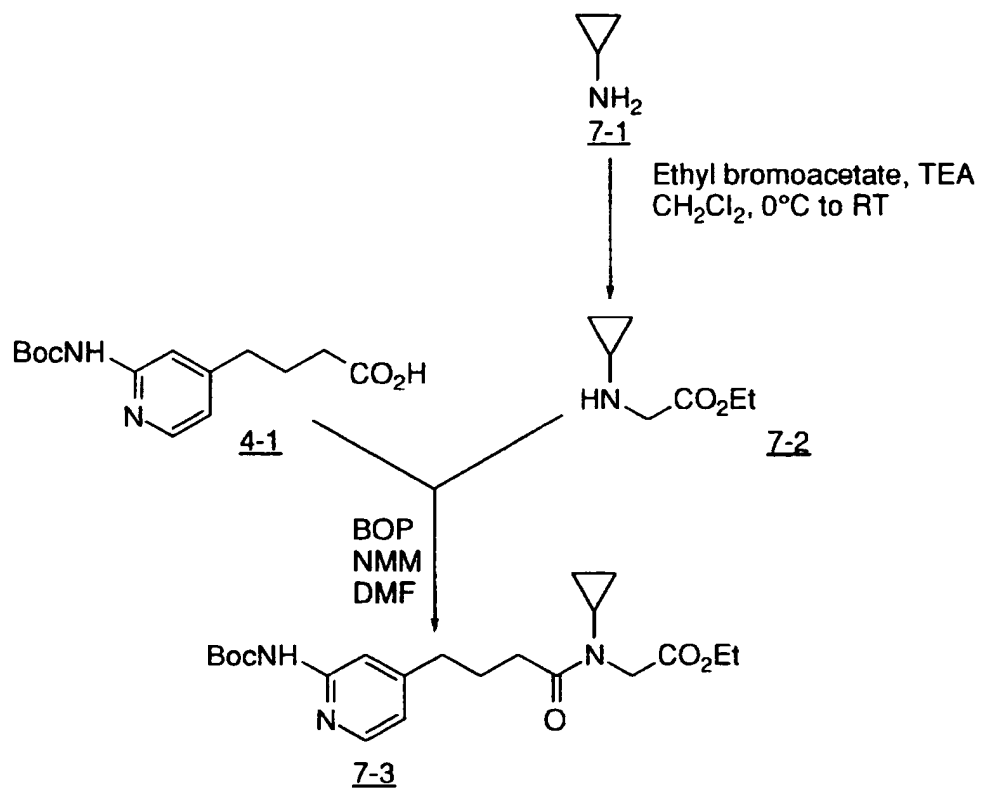
Ester 6-3 (400 mg, 0.84 mmol) was dissolved in 4 mL EtOH, then 1 N NaOH (1.7 mL, 1.7 mmol) was added. After 90 min the reaction was neutralized with 1 N HCl (1.7 mL, 1.7 mmol) and concentrated to an oil. Flash chromatography (silica, 50:1:1 EtOH/H₂O/NH₄OH, then again with 12:10:1:1 EtOAc/EtOH/H₂O/NH₄OH) provided 6-4.

15 TLC R_f 0.17 (silica, 12:10:1:1 EtOAc/EtOH/H₂O/NH₄OH)

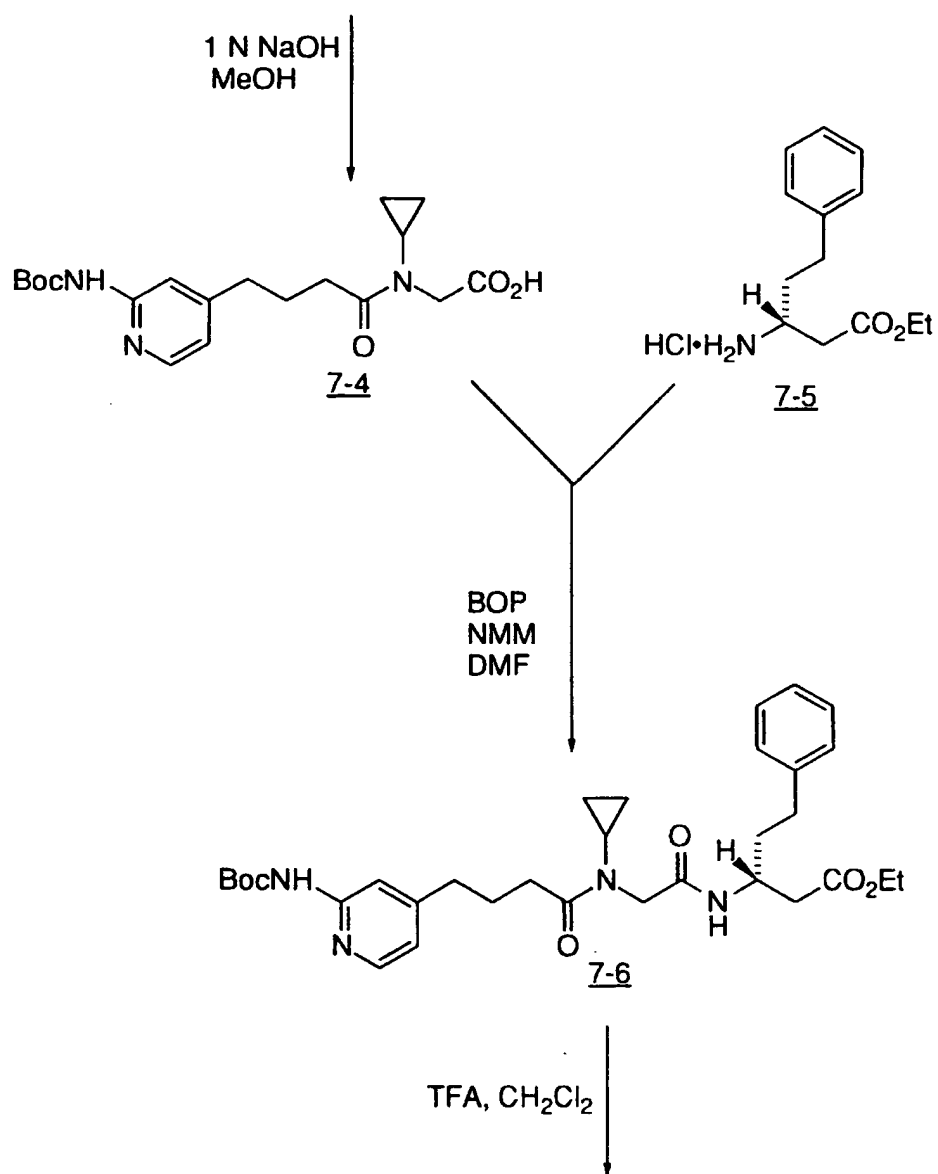
¹H-NMR (400 MHz, CD₃OD): 2:1 mixture of amide rotomers, δ 8.38-8.28 (m, 2H), 7.54-7.48 (m, 1H), 7.30-7.25 (m, 2H), 7.21-7.19 (m, 1H), 7.07-6.92 (m, 3H), 4.36-4.27 (m, 1H), 4.03-3.98 (m, 2H), 3.06/2.93 (s, 3H), 2.86-2.60 (m, 4H), 2.52-2.32 (m), 2.05-1.85 (m).

20

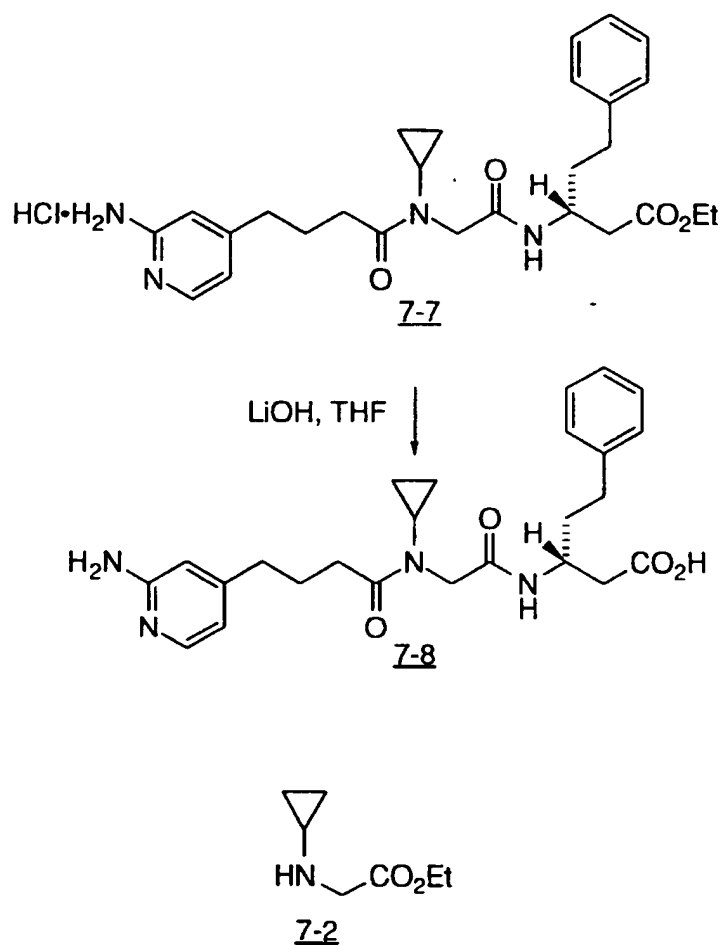
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SCHEME 7

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SCHEME 7 (CONT'D)

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SCHEME 7 (CONTD)

5

N-Cyclopropylglycine ethyl ester (7-2)

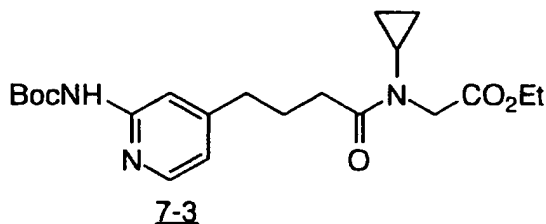
- Cyclopropylamine (12.1 mL, 175 mmol) and TEA (42 mL, 385 mmol) were combined at 0°C in 350 mL CH_2Cl_2 , then ethyl bromoacetate (19.4 mL, 175 mmol) was added dropwise. The reaction was warmed to RT for 3 h, then diluted with additional CH_2Cl_2 , washed with water, sat. NaHCO_3 , and brine, dried (Na_2SO_4), filtered and concentrated. Flash filtration (silica, 30 % EtOAc/hexane) provided 7-2 as a light yellow oil.

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TLC R_f 0.70 (silica, EtOAc)

¹H-NMR (400 MHz, CDCl₃): δ 4.20 (q, J = 7 Hz, 2H), 3.45 (s, 2H), 2.23 (tt, J = 6, 3 Hz, 1H), 1.29 (t, J = 7 Hz, 3H), 0.43 (m, 2H), 0.36 (m, 2H).

5



4-(2-Boc-amino-pyridin-4-yl)butanoyl-N-cyclopropylglycine ethyl ester (7-3)

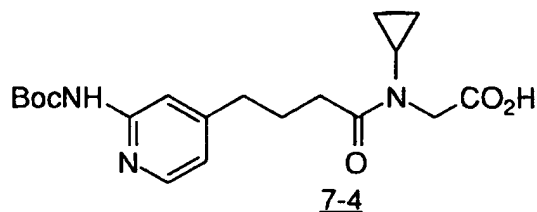
10 Acid 4-1 (0.86 g, 3.1 mmol), amine 7-2 (0.48 g, 3.4 mmol), NMM (1.35 mL, 12.3 mmol) and BOP (2.04 g, 4.61 mmol) were combined in 15 mL DMF. After stirring overnight the mixture was concentrated, redissolved in EtOAc, washed with water, 5 % KHSO₄, sat. NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (silica, 50 % EtOAc/hexane) provided 7-3 as a colorless oil.

15 TLC R_f 0.29 (silica, 50 % EtOAc/hexane)

¹H-NMR (400 MHz, CDCl₃): δ 8.14 (d, J = 5 Hz, 1H), 7.81 (s, 1H), 7.77 (br s, 1H), 6.84 (dd, J = 5, 1 Hz, 1H), 4.18 (q, J = 7 Hz, 2H), 4.08 (s, 2H), 2.80 (tt, J = 7, 4 Hz, 1H), 2.69 (t, J = 7 Hz, 2H), 2.60 (t, J=7 Hz, 2H), 2.02 (qn, J = 7 Hz, 2H), 1.53 (s, 9H), 1.27 (t, J = 7 Hz, 3H), 0.83 (m, 2H), 0.72 (m, 2H).

20

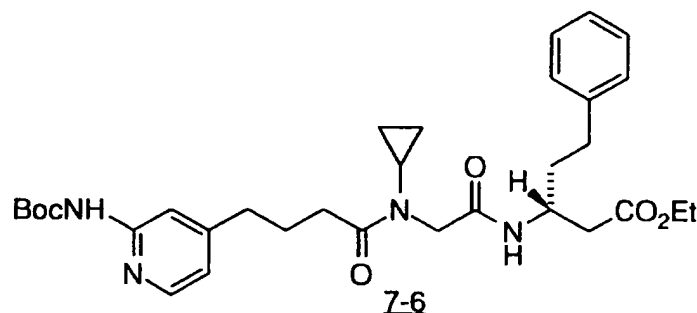
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4-(2-Boc-amino-pyridin-4-yl)butanoyl-N-cyclopropylglycine (7-4)

- 5 Ester 7-3 (1.07 g, 2.64 mmol) was dissolved in 26 mL MeOH, then treated with 1 N NaOH (6.6 mL, 6.6 mmol). After stirring overnight the reaction was concentrated, redissolved in water, the pH was adjusted to 1 with 10 % KHSO₄, then extracted with EtOAc (5x). The aqueous phase was adjusted to pH 3 with aq. NaOH, then
- 10 reextracted with EtOAc (2x). The combined organic phases were washed with brine, dried (MgSO₄), filtered and concentrated, providing 7-4 as a white foam.
- TLC R_f 0.24 (silica, 19:1:1, CH₂Cl₂/MeOH/HOAc)
- ¹H-NMR (300 MHz, CDCl₃): δ 9.15 (br s, 1H), 7.97 (d, J = 5 Hz, 1H),
- 15 7.94 (s, 1H), 6.89 (dd, J = 5, 1 Hz, 1H), 4.14 (s, 2H), 2.81 (tt, J = 7, 3 Hz, 1H), 2.73 (t, J = 7 Hz, 2H), 2.61 (t, J = 7 Hz, 2H), 2.04 (qn, J = 7 Hz, 2H), 1.51 (s, 9H), 0.85 (m, 2H), 0.76 (m, 2H).

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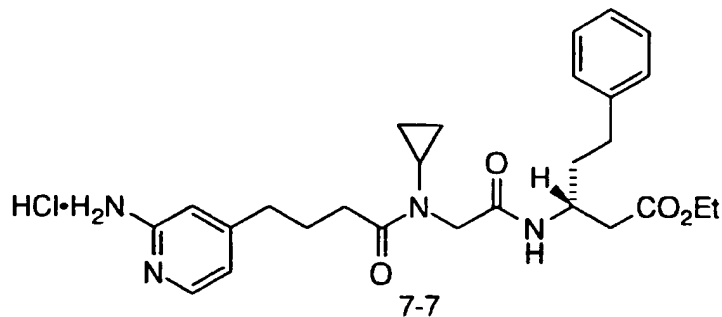


4-(2-Boc-amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)-β-alanine ethyl ester (7-6)

- 5 Acid 7-4 (415 mg, 1.1 mmol), amine hydrochloride 7-5
 (see procedure in EP 478 362 utilizing Boc-Gly(OEt) as starting
 material) (284 mg, 1.1 mmol), NMM (0.48 mL, 4.4 mmol) and BOP
 (729 mg, 1.65 mmol) were combined in 5 mL DMF. After stirring
 overnight the reaction was concentrated, redissolved in EtOAc, washed
 10 with water, 5 % KHSO₄, sat. NaHCO₃, and brine, dried (MgSO₄),
 filtered and concentrated. Flash chromatography (silica, EtOAc)
 provided 7-6 as a colorless waxy solid.
 TLC R_f 0.39 (silica, EtOAc)
¹H-NMR (400 MHz, d₆-DMSO): δ 9.66 (s, 1H), 8.11 (d, J = 5 Hz, 1H),
 15 7.76 (d, J = 9 Hz, 1H), 7.68 (s, 1H), 7.25 (t, J = 7 Hz, 2H), 7.20-7.12
 (m, 3H), 6.88 (dd, J = 5, 1 Hz, 1H), 4.01 (q, J = 7 Hz, 2H), 3.91 (AB d,
 J = 16 Hz, 1H), 3.83 (AB d, J = 16 Hz, 1H), 3.32 (s, 2H), 2.78 (m, 1H),
 2.65-2.40 (m), 1.86-1.77 (m), 1.46 (s, 9H), 1.14 (t, J = 7 Hz, 3H), 0.77-
 0.70 (m, 4H).

20

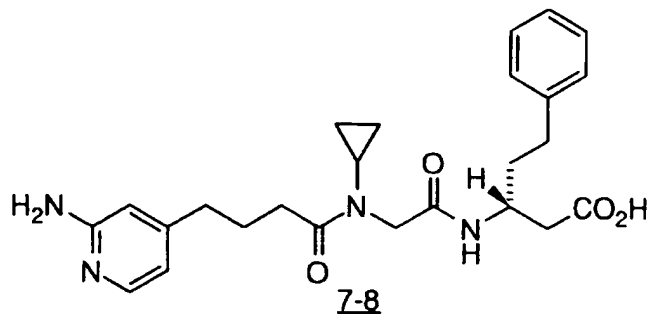
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4-(2-Amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)-β-alanine ethyl ester hydrochloride (7-7)

- A solution of 7-6 (530 mg, 0.91 mmol) in 4.6 mL CH₂Cl₂ was cooled to 0°C, 4.6 mL TFA was added, and after 1 h the reaction was warmed to RT for 90 min. After concentration and azeotroping with toluene the residue was purified by flash chromatography (silica, 10:1, EtOAc:NH₃-saturated EtOH). The residue was dissolved in EtOAc, treated with 1 N HCl in ether, concentrated, then lyophilized from aq. acetonitrile, providing 7-7 as a glassy solid.
- TLC R_f 0.25 (10:1, EtOAc:NH₃-saturated EtOH)
- ¹H-NMR (400 MHz, d₆-DMSO): δ 7.94 (br s, 1H), 7.86-7.82 (m, 2H), 7.25 (t, J = 7 Hz, 2H), 7.20-7.13 (m, 3H), 6.80-6.75 (m, 2H), 4.05 (m), 4.02 (q, J = 7 Hz, 2H), 3.93 (AB d, J = 16 Hz, 1H), 3.85 (AB d, J = 16 Hz, 1H), 2.78 (qn, 1H), 2.65 (t, J = 7 Hz, 2H), 2.59 (t, J = 7 Hz, 2H), 2.55-2.40 (m), 1.82 (qn, J = 7 Hz, 2H), 1.80-1.70 (m, 2H), 1.15 (t, J = 7 Hz, 3H), 0.80-0.70 (m, 4H).

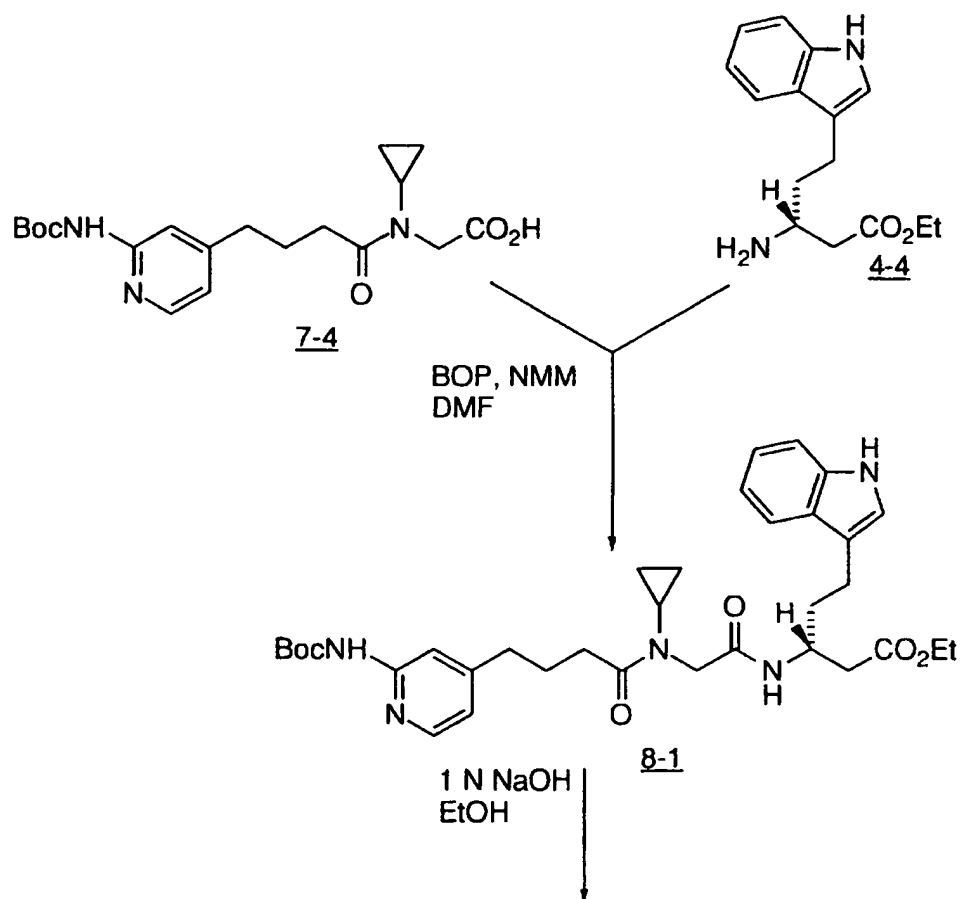
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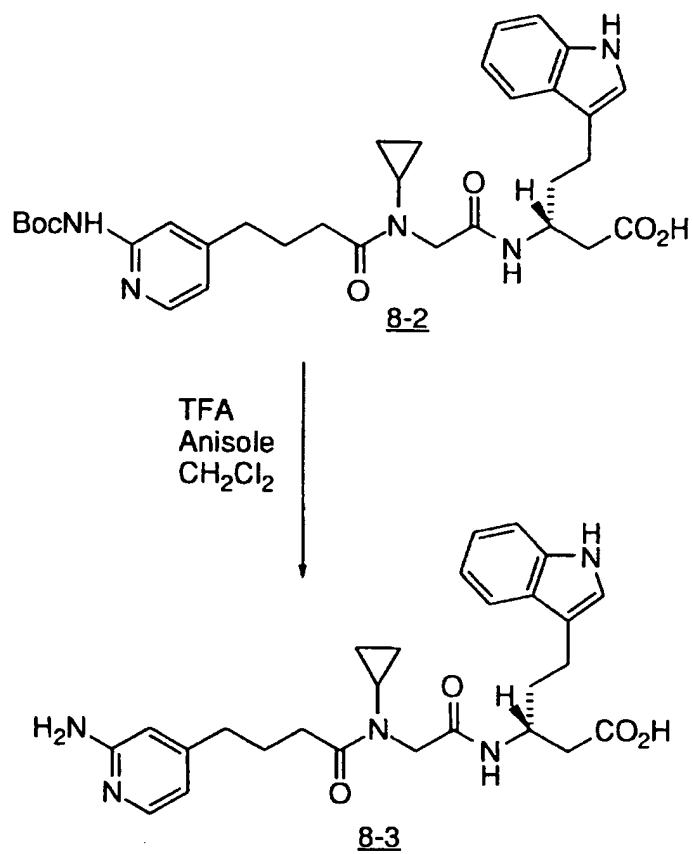
4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)-β-alanine (7-8)

- Ester 7-7 (100 mg, 0.18 mmol) was dissolved in 4 mL THF, then treated with 1 N LiOH (0.9 mL, 0.9 mmol). After stirring overnight the mixture was concentrated and purified by flash chromatography (silica, 15:20:1:1 EtOAc/EtOH/H₂O/NH₄OH) to provide 7-8 as a white solid.
- TLC R_f 0.36 (silica, 15:20:1:1 EtOAc/EtOH/H₂O/NH₄OH)
- 10 ¹H-NMR (400 MHz, d₆-DMSO): δ 7.81 (d, J = 9 Hz, 1H), 7.77 (d, J = 5 Hz, 1H), 7.27 (t, J = 7 Hz, 2H), 7.20-7.12 (m, 3H), 6.34 (dd, J = 5, 1 Hz, 1H), 6.28 (s, 1H), 5.76 (br s, 2H), 4.03 (m, 1H), 3.91 (AB d, J = 16 Hz, 1H), 3.85 (AB d, J = 16 Hz, 1H), 2.76 (m, 1H), 2.65-2.50 (m), 2.45 (t, J = 7 Hz, 2H), 2.37 (d, J = 7 Hz, 2H), 1.82-1.60 (m), 0.77-0.68 (m,
- 15 4H).

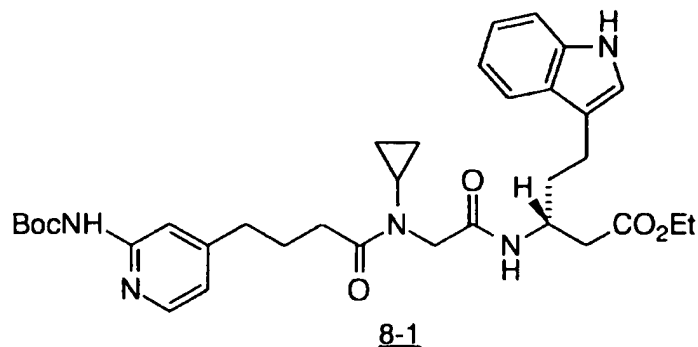
- 89 -

SCHEME 8

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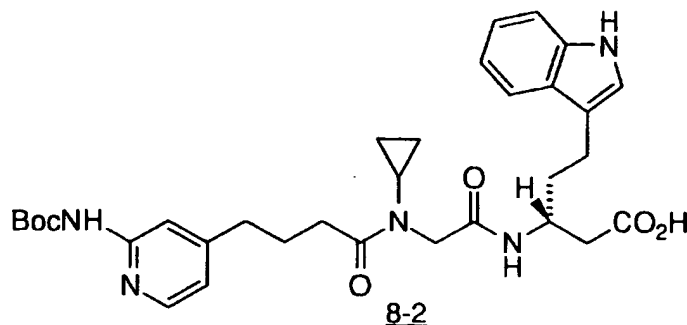
4-(2-Boc-amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-[2-(indol-3-yl)ethyl]-β-alanine ethyl ester (8-1)

- Acid 7-4 (180 mg, 0.48 mmol), amine 4-4 (130 mg, 0.50 mmol), NMM (183 μ L, 1.7 mmol) and BOP (253 mg, 0.57 mmol) were combined in 5 mL DMF. After stirring overnight the reaction was concentrated, redissolved in EtOAc, washed with water (3x), 10 % KHSO₄, sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 80 % EtOAc/hexane) provided 8-1 as a glassy solid.

TLC R_f 0.34 (silica, EtOAc)

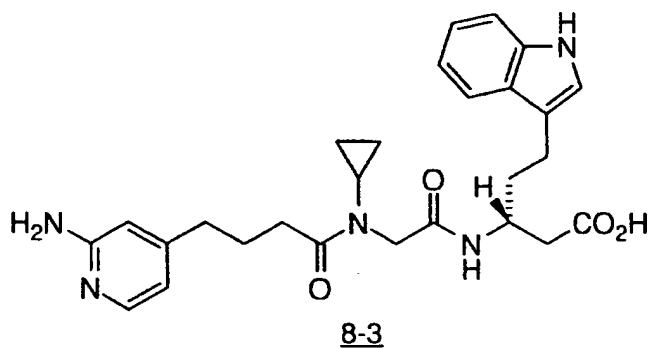
- ¹H-NMR (400 MHz, CDCl₃): δ 8.10-8.00 (m, 2H), 7.79 (s, 1H), 7.56 (d, J = 8 Hz, 1H), 7.35-7.30 (m, 2H), 7.16 (t, J = 8 Hz, 1H), 7.08 (t, J = 8 Hz, 1H), 7.04 (s, 1H), 6.80 (d, J = 5 Hz, 1H), 6.71 (d, J = 9 Hz, 1H), 4.29 (m, 1H), 4.09 (q, J = 7 Hz, 2H), 3.99 (s, 2H), 2.85-2.70 (m, 4H), 2.66 (t, J = 7 Hz, 2H), 2.61 (t, J = 7 Hz, 2H), 2.51 (m), 2.05-1.87 (m, 4H), 1.53 (s, 9H), 1.21 (t, J = 7 Hz, 3H), 0.90-0.75 (m, 4H).

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4-(2-Boc-amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-[2-(indol-3-yl)ethyl]-β-alanine (8-2)

- Ester 8-1 (223 mg, 0.36 mmol) was dissolved in 4 mL EtOH, then 1 N NaOH (0.90 mL, 0.90 mmol) was added. After a few hours the reaction was diluted with EtOAc, extracted with water and the pH of the aq. phase was adjusted to 1 with 10 % KHSO₄. The aqueous layer was extracted with EtOAc (2x), the combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated, providing 8-2 as an oil.
- TLC R_f 0.64 (silica, 9:1:1 CH₂Cl₂/MeOH/HOAc)



- 4-(2-Amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-[2-(indol-3-yl)ethyl]-β-alanine (8-3)

Acid 8-2 (144 mg, 0.24 mmol) was dissolved in 3 mL CH₂Cl₂, then anisole (120 μL, 0.96 mmol) and TFA (3 mL) were added. After ca 1 h the reaction was concentrated. Flash

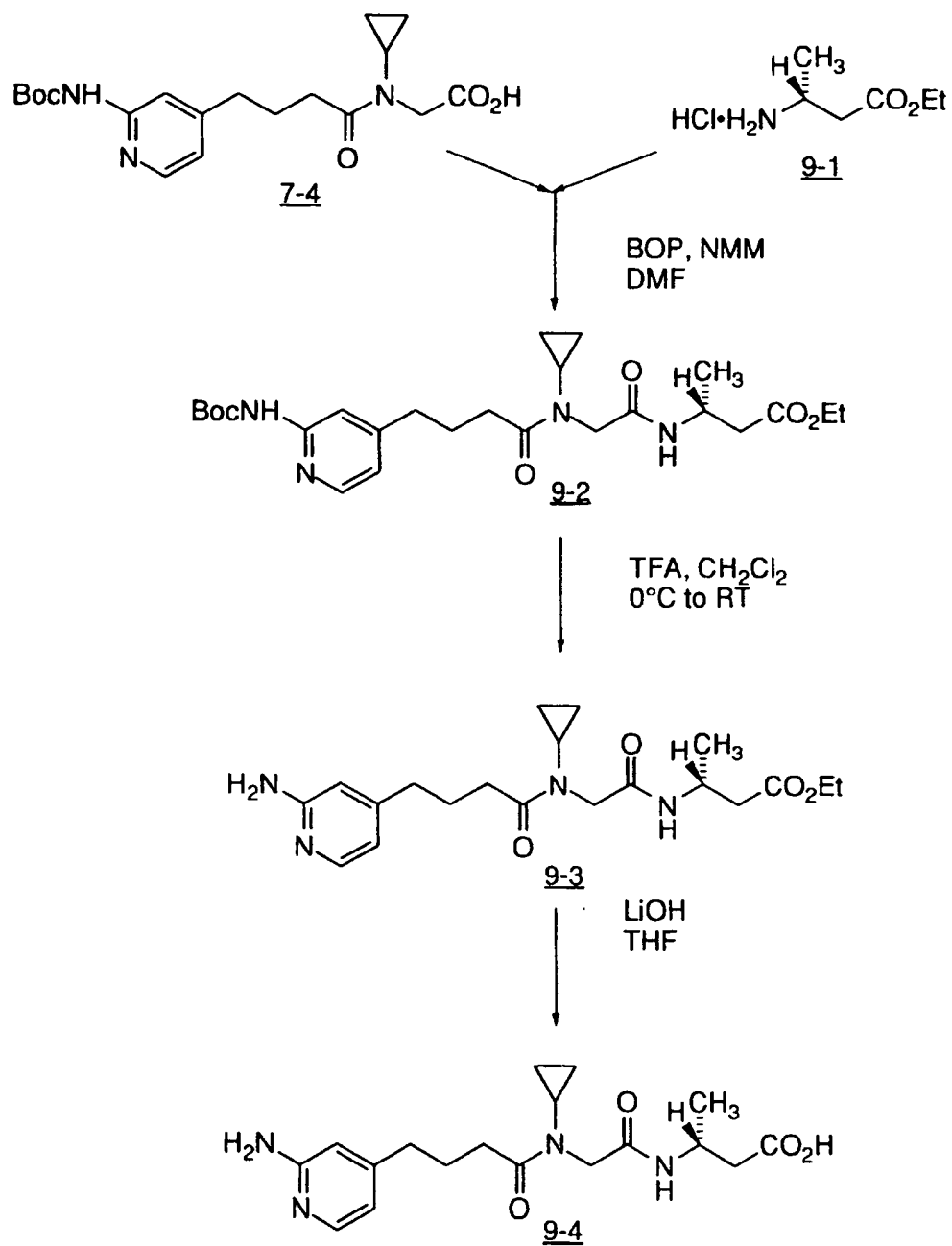
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chromatography (silica, 18:10:1:1 EtOAc/EtOH/H₂O/NH₄OH, twice)
provided 8-3 as a white solid.

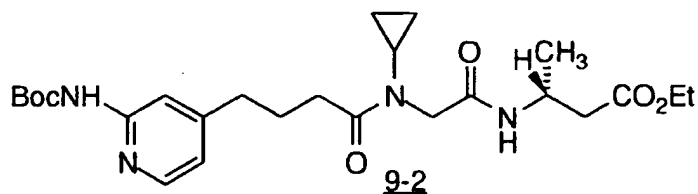
TLC R_f 0.29 (silica, 18:10:1:1 EtOAc/EtOH/H₂O/NH₄OH)

¹H-NMR (400 MHz, D₂O): δ 7.88 (m, 1H), 7.70 (m, 1H), 7.53 (m, 1H),
5 7.30-7.10 (m, 3H), 6.69 (m, 1H), 6.58 (m, 1H), 4.23 (m, 1H), 3.99 (m,
2H), 2.84 (m, 3H), 2.70 (m, 2H), 2.62 (m, 2H), 2.44 (m), 2.10-1.82
(m), 0.88-0.72 (m, 4H).

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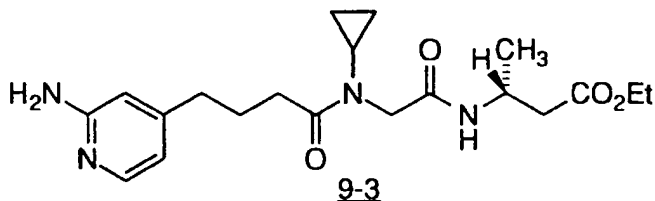
SCHEME 9

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4-(2-Boc-amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester (9-2)

- Acid 7-4 (100 mg, 0.26 mmol), amine hydrochloride 9-1 (see United States Patent 5,281,585) (49 mg, 0.29 mmol), NMM (117 μ L, 1.1 mmol) and BOP (176 mg, 0.40 mmol) were combined in 1.3 mL DMF. After 3 d the mixture was concentrated, redissolved in EtOAc, washed with water (2x), 5 % KHSO₄, sat. NaHCO₃, and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, EtOAc) provided 9-2 as a colorless oil. TLC R_f 0.27 (silica, EtOAc) ¹H-NMR (400 MHz, CDCl₃): δ 8.10 (d, J = 5 Hz, 1H), 8.00 (br s, 1H), 7.85 (s, 1H), 6.90 (dd, J = 5, 1 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 4.30 (m, 1H), 4.12 (q, J = 7 Hz, 2H), 4.02 (AB d, J = 15 Hz, 1H), 3.93 (AB d, J = 15 Hz, 1H), 2.77 (m, 1H), 2.73 (t, J = 7 Hz, 2H), 2.62 (t, J = 7 Hz, 2H), 2.47 (m, 2H), 2.04 (m, 2H), 1.53 (s, 9H), 1.25 (t, J=7 Hz, 3H), 1.20 (d, J = 7 Hz, 3H), 0.88-0.78 (m, 4H).



- 4-(2-Amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester (9-3)

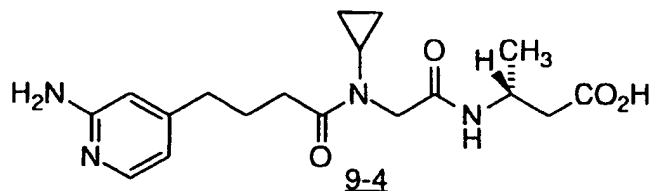
A solution of 9-2 (84 mg, 0.17 mmol) in 1 mL CH₂Cl₂ at 0°C was treated with 1 mL TFA. After 3 h the mixture was warmed to RT for 1 h, then concentrated and azeotroped with toluene. Flash

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chromatography (silica, 15 % NH₃ satd. i-PrOH/EtOAc) and lyophilization from aq. acetonitrile provided 9-3 as a semi-solid.

TLC R_f 0.19 (silica, 15 % NH₃ satd. i-PrOH/EtOAc)

¹H-NMR (400 MHz, d₆-DMSO): δ 7.78 (d, J = 5 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 6.37 (dd, J = 5, 1 Hz, 1H), 6.30 (s, 1H), 5.90 (br s, 1H), 4.09 (m, J = 7 Hz, 1H), 4.04 (q, J = 7 Hz, 2H), 3.86 (AB d, J = 16 Hz, 1H), 3.79 (AB d, J = 16 Hz, 1H), 2.73 (m, 1H), 2.45 (t, J = 7 Hz, 2H), 2.35 (ABX dd, J = 15, 7 Hz, 1H), 1.77 (qn, J = 7 Hz, 2H), 1.17 (t, J = 7 Hz, 3H), 1.07 (d, J = 7 Hz, 3H), 0.76-0.67 (m, 4H).

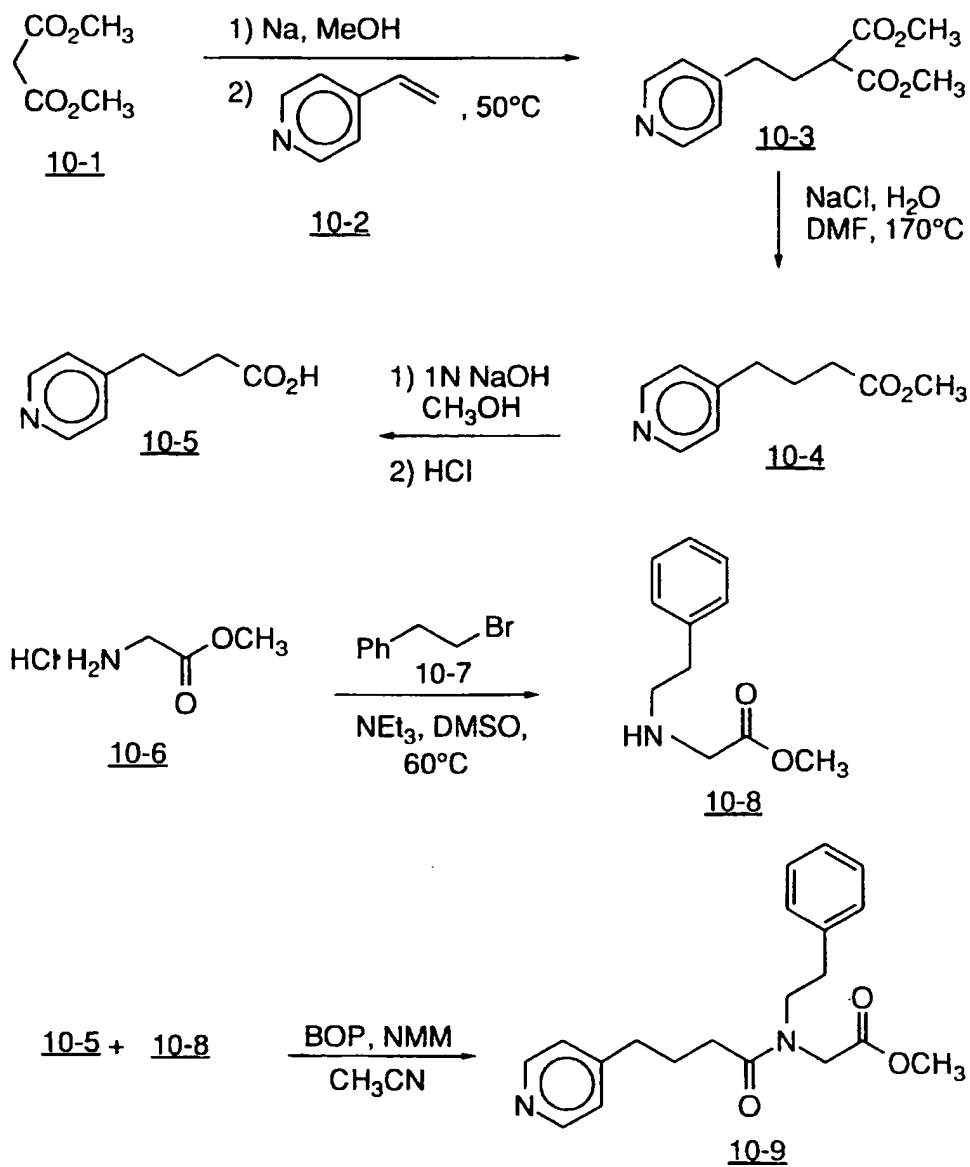


4-(2-Amino-pyridin-4-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl-β-alanine (9-4)

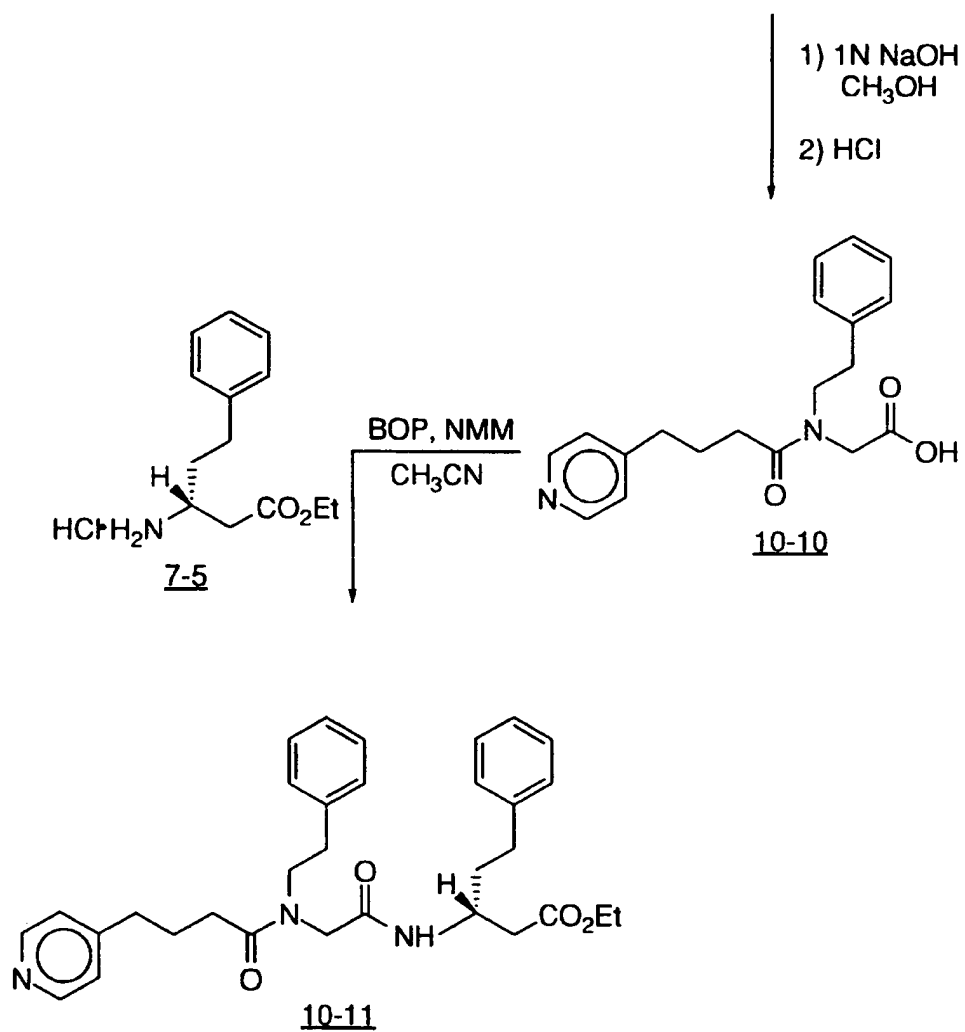
Ester 9-3 (44 mg, 0.11 mmol) was dissolved in 1.1 mL THF, then 1 N LiOH (0.28 mL, 0.28 mmol) was added. After stirring overnight the reaction mixture was loaded directly onto a flash chromatography column (silica, eluting with 7:20:1:1 EtOAc/EtOH/H₂O/NH₄OH) providing 9-4 as a white solid. TLC R_f 0.62 (silica, 7:20:1:1 EtOAc/EtOH/H₂O/NH₄OH)

¹H-NMR (300 MHz, D₂O): δ 7.72 (d, J = 7 Hz, 1H), 6.90-6.80 (m, 2H), 4.16 (hex, J = 7 Hz, 1H), 4.04 (s, 2H), 2.86 (tt, J = 7, 4 Hz, 1H), 2.80-2.65 (m, 4H), 2.41 (ABX dd, J = 14, 6 Hz, 1H), 2.31 (ABX dd, J = 14, 7 Hz, 1H), 1.98 (qn, J = 7 Hz, 2H), 1.16 (d, J = 7 Hz, 3H), 0.89 (m, 2H), 0.80 (m, 2H).

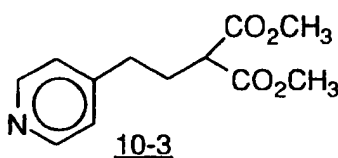
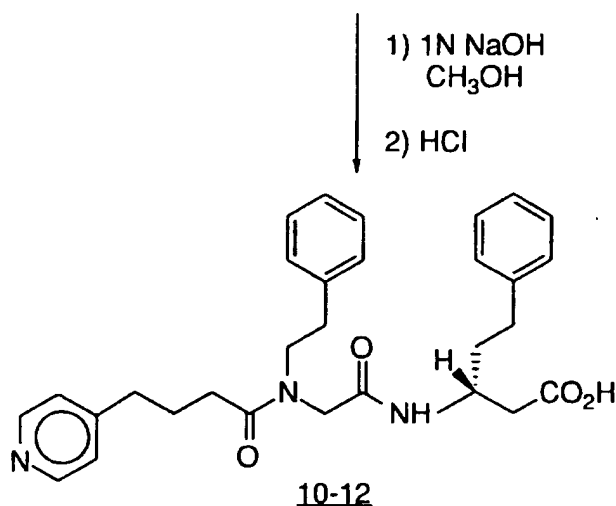
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SCHEME 10

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SCHEME 10 CONTINUED

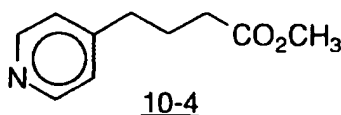
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5 Methyl 2-(methoxycarbonyl)-4-(pyridin-4-yl)butyrate (10-3)

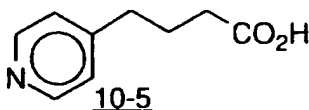
- To a stirred solution of elemental sodium (20 g, 840 mmol) and CH₃OH (600 ml) was added dimethyl malonate 10-1 (135 ml, 1120 mmol). After 5 minutes, 4-vinyl pyridine 10-2 (15.3 ml, 140 mmoles) was added and the solution was heated to 50°C for 18 h. The reaction
- 10 was diluted with EtOAc and then washed with sat NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) furnished the diether 10-3 (19.1 g) as a yellow oil. TLC R_f = 0.43 (silica, EtOAc)
- ¹H NMR (400 MHz, CDCl₃) δ 8.52 (d, J = 6 Hz, 2H), 7.12 (d, J = 6 Hz, 2H), 3.75 (s, 6H), 3.38 (t, J = 8 Hz, 1H), 2.64 (t, J = 8 Hz, 2H), 2.24 (m, 2H).
- 15

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Methyl 4-(Pyridin-4-yl)butyrate (10-4)

- A solution of diester 10-3 (19.0 g, 80.1 mmol), H₂O (1.45 ml, 80.1 mmol), NaCl (10.5 g, 160.2 mmol) and DMF was heated to 170°C for 18 h. The reaction was diluted with EtOAc and then washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 60% EtOAc/hexanes) afforded ester 10-4 as a brown oil.
- 5
- 10 TLC R_f 0.32 (silica, EtOAc)
¹H NMR (400 MHz, CD₃OD) δ 8.40 (d, J = 6 Hz, 2H), 7.28 (d, J = 6 Hz, 2H), 3.64 (s, 3H), 2.67 (t, J = 8 Hz, 2H), 2.36 (t, J = 8 Hz, 2H), 1.94 (m, 2H).

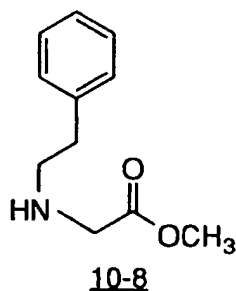


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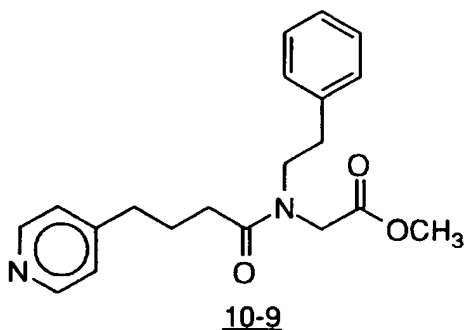
4-(Pyridin-4-yl)butanoic acid (10-5)

- A solution of ester 10-4 (10.0 g, 56 mmol), 1N NaOH (84 ml, 84 mmole) and CH₃OH (200 ml) was stirred at ambient temperature for 1.0 h. Concentrated HCl (7.0 ml, 84 mmol) was added followed by concentration. The residue was dissolved in CHCl₃, dried (MgSO₄) and concentrated to give acid 10-5 as a yellow solid.
- 20
- TLC R_f 0.41 (silica 10:1:1 CH₂Cl₂/MeOH/AcOH)
¹H NMR (400 MHz, CD₃OD) δ 8.40 (d, J = 6 Hz, 2H), 7.30 (d, J = 6 Hz, 2H), 2.71 (t, J = 8 Hz, 2H), 2.32 (t, J = 7 Hz, 2H), 1.93 (m, 2H).
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N-(2-Phenethyl)glycine methyl ester (10-8)

- A solution of amine methyl ester 10-6 (1.0 g, 7.96 mmol),
 5 bromide 10-7 (1.09 ml, 7.96 mmole), NEt₃ (3.33 ml, 23.9 mmol) and
 DMSO (25 ml) was heated to 60°C for 16 h. The reaction mixture was
 diluted with EtOAc and then washed with sat. NaHCO₃, brine, dried
 (MgSO₄) and concentrated. Flash chromatography (silica, 80%
 EtOAc/hexanes) furnished ester 10-8 as a yellow oil.
 10 TLC R_f 0.29 (silica, EtOAc)
¹H NMR (400 MHz, CDCl₃) δ 7.29 (m, 2H), 7.22 (m, 3H), 3.71 (s, 3H),
 3.43 (s, 2H), 2.89 (m, 2H), 2.82 (m, 2H).



15 4-(Pyridin-4-yl)butanoyl-N-(2-phenethyl)glycine methyl ester (10-9)

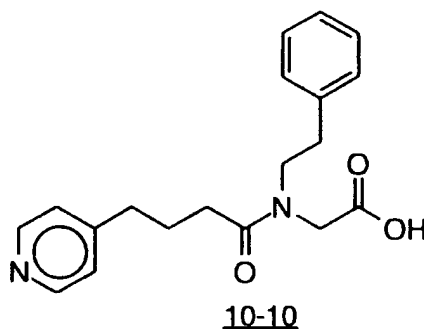
- To a stirred solution of acid 10-5 (342 mg, 2.07 mmol),
 NMM (910 µl, 8.28 mmol) and CH₃CN (15 ml) was added BOP reagent
 (1.01 g, 2.28 mmol). After 30 minutes, amine 10-8 (400 mg, 2.07
 20 mmol) was added and stirring continued for an additional 18 h. The

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reaction was diluted with EtOAc and then washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, EtOAc) furnished ester 10-9 as a yellow oil.

TLC R_f = 0.23 (silica, EtOAc)

- 5 ¹H NMR (CD₃OD) 8.39 (d, J = 8 Hz, 2H), 7.14-7.29 (m, 7H), 4.84 (s, 2H), 3.70 (s, 3H), 3.58 (t, J = 7 Hz, 2H), 2.82 (t, J = 7 Hz, 2H), 2.66 (t, J = 8 Hz, 0.56 H), 2.55 (t, J = 8 Hz, 1.44 H), 2.28 (t, J = 7 Hz, 0.56 H), 2.10 (t, J = 7Hz, 1.44 H).



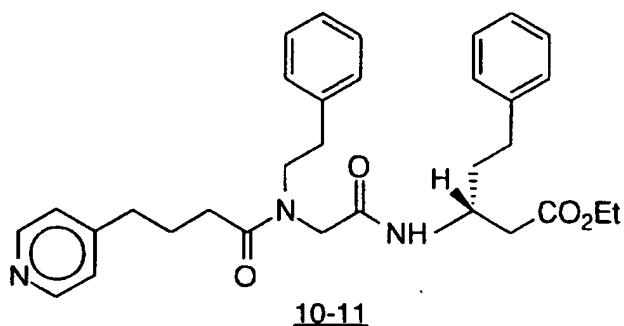
10

4-(Pyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl (10-10)

- 15 A solution of ester 10-9 (500 mg, 1.47 mmole), 1N NaOH (2 ml, 2 mmol) and CH₃OH (5 ml) was stirred at ambient temperature for 2.0 h. Concentrated HCl (167 μ l, 2.0 mmol) was added followed by concentration. The residue was dissolved in CHCl₃, dried (MgSO₄) and concentrated to give acid 10-10 as a white solid.

- 20 ¹H NMR (400 MHz, CD₃OD) δ 8.47 (d, J = 5 Hz, 2H), 7.44 (m, 2H), 7.25 (m, 5H), 4.02 (s, 1.44 H), 3.96 (s, 0.56 H), 3.58 (m, 2H), 2.84 (m, 2H), 2.74 (t, J = 8 Hz, 0.56 H), 2.63 (t, J = 8 Hz, 1.44 H), 2.33 (t, J = 7Hz, 0.56 H), 2.14 (t, J = 7 Hz, 1.44 H), 1.94 (m, 0.56 H), 1.79 (m, 1.44 H).

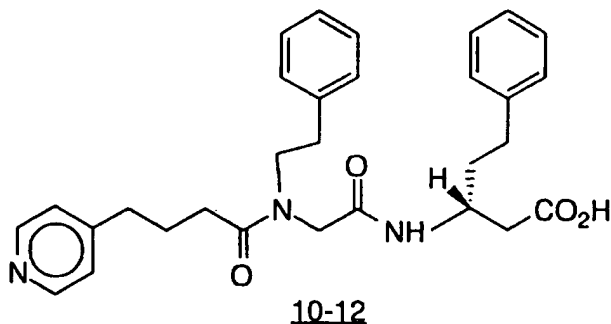
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4-(Pyridin-4-yl)butanoyl-N-(2-phenylethyl)glycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester (10-11)

- 5 A solution of acid 10-10 (160 mg, 0.4903 mmol) amine 7-5 (164 mg, 0.49 mmol), NMM (216 μ l, 1.96 mmol), BOP reagent (239 mg, 0.539 mmol) and CH₃CN (5 ml) was stirred at ambient temperature for 18 h. The reaction was diluted with EtOAc and then washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash
- 10 chromatography (silica, EtOAc) furnished ester 10-11 (220 mg) as a colorless oil.
- TLC R_f = 0.21 (silica, EtOAc)
- ¹H NMR (400 MHz, CD₃OD) δ 8.37 (m, 2H), 7.24 (m, 12H), 4.23 (m, 1H), 4.06 (m, 2H), 3.95 (m, 2H), 2.84 (m, 2H), 2.56 (m, 6H), 2.34 (t, J = 7 Hz, 0.56H), 2.16 (t, J = 7 Hz, 1.44 H), 1.83 (m, 0.56 H), 1.81 (m, 1.44 H), 1.91 (m, 3H).
- 15

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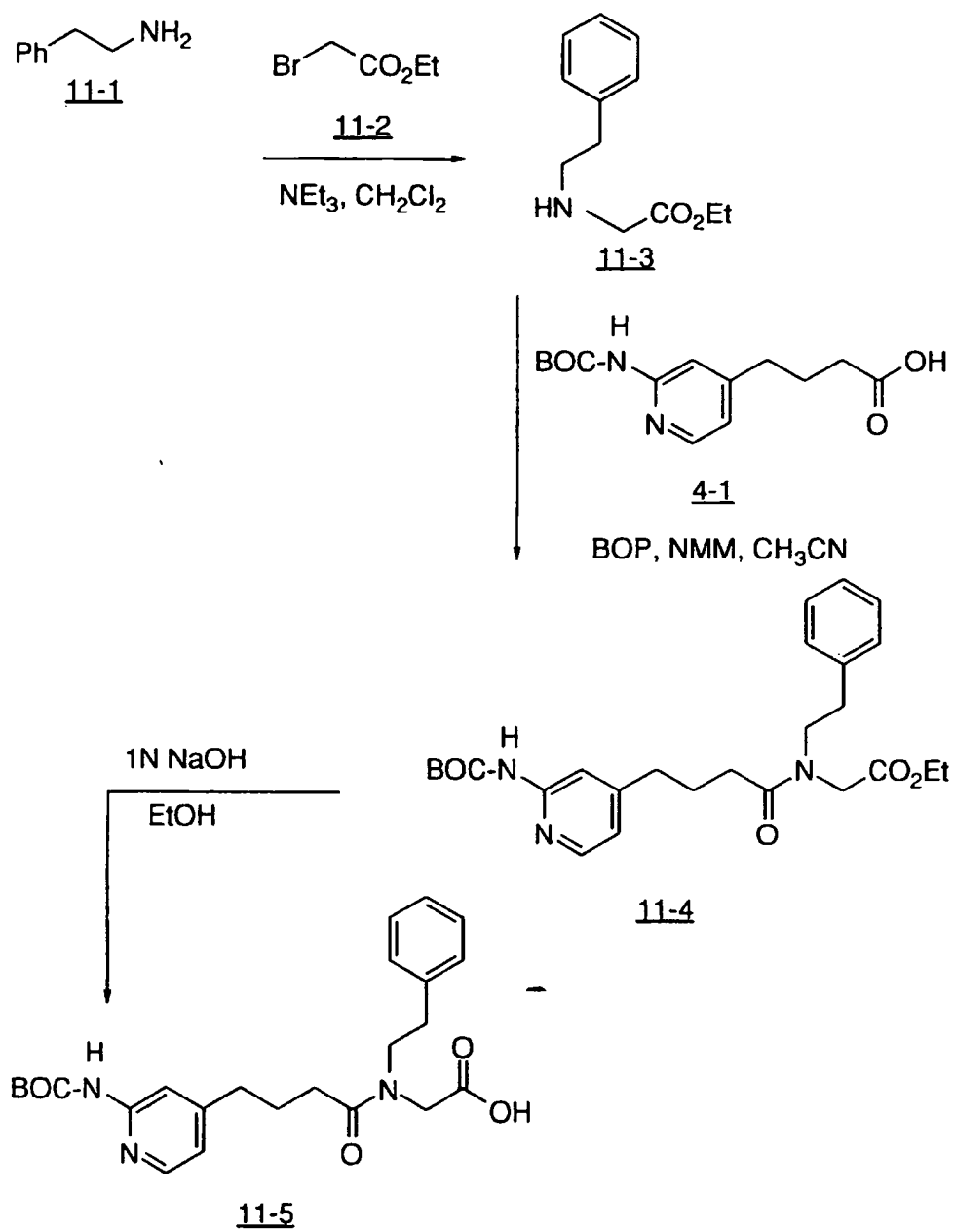


4-(Pyridin-4-yl)butanoyl-N-(2-phenyl)glycyl-3(R)-(2-phenethyl)-β-alanine (10-12)

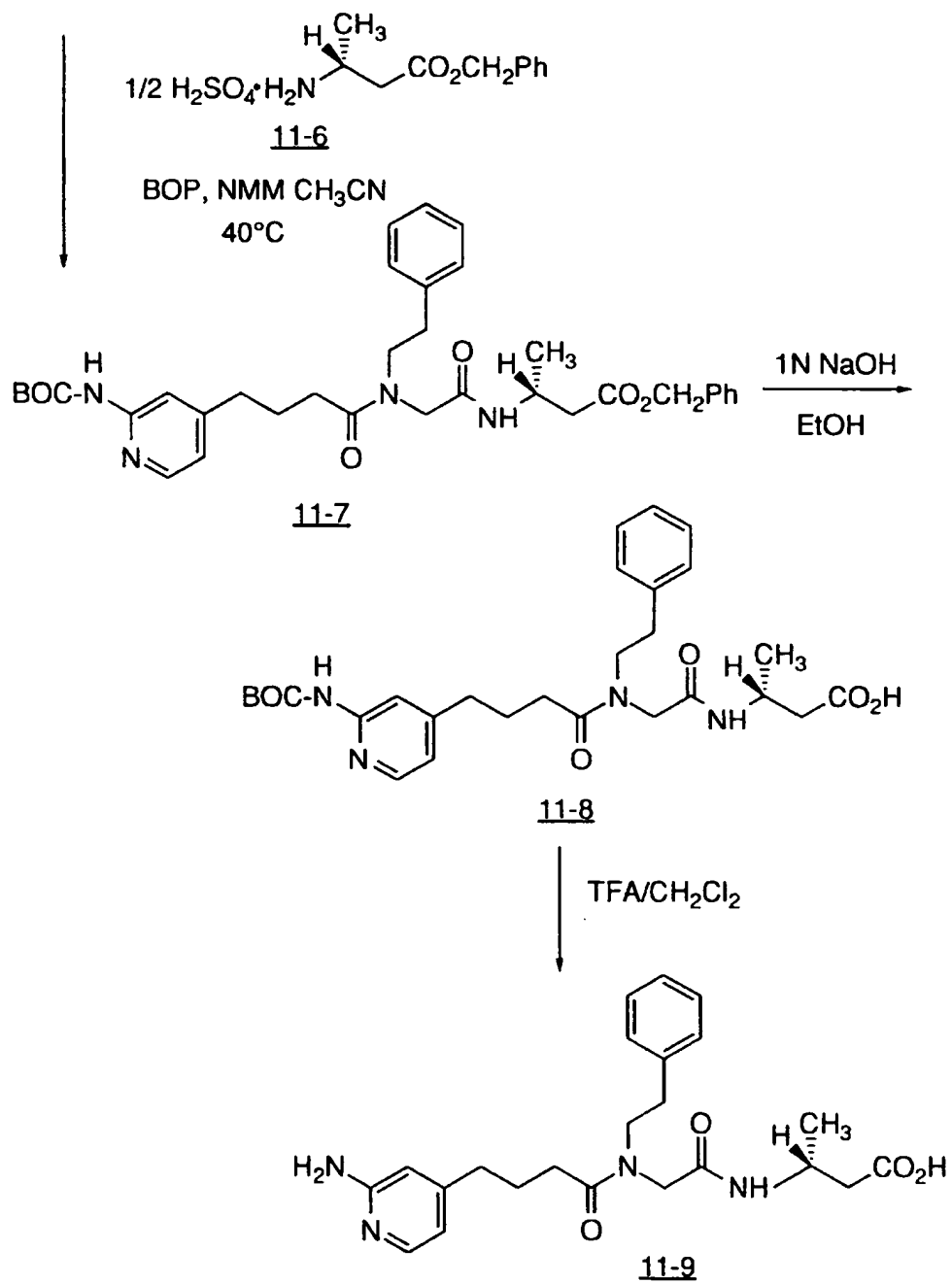
- 5 A solution of ester 10-11 (200 mg, 0.3778 mmole), 1N NaOH (0.5 ml, 0.5 mmol) and CH₃OH was stirred at ambient temperature for 1.5 h followed by concentration. The crude acid was dissolved in H₂O, acidified with conc. HCl, concentrated and then azeotroped with toluene. Flash chromatography (silica, 20:20:1:1
- 10 EtOAc/EtOH/NH₄OH/H₂O) furnished acid 10-12 (100 mg) as a white solid.
- TLC R_f 0.18 (20:20:1:1 EtOAc/EtOH/NH₄OH/H₂O)
- ¹H NMR (400 MHz, D₂O) δ 8.47 (d, J = 6 Hz, 1.36 H), 8.43 (d, J = 6 Hz, 0.64 H), 7.71 (d, J = 6 Hz, 0.64 H), 7.66 (d, J = 6 Hz, 1.36 H), 7.20
- 15 (m, 10 H), 4.07 (m, 1H), 3.81 (s, 1.36 H), 3.73 (d, J = 6 Hz, 0.64 H), 3.51 (bt, 1.36 H), 3.43 (m, 0.64 H), 2.73 (m, 3H), 2.60 (t, J = 7 Hz, 1.36 H), 2.53 (m, 3.64 H), 2.18 (t, J = 7 Hz, 0.64 H), 1.78 (m, 5.36 H).

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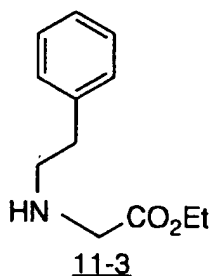
SCHEME 11



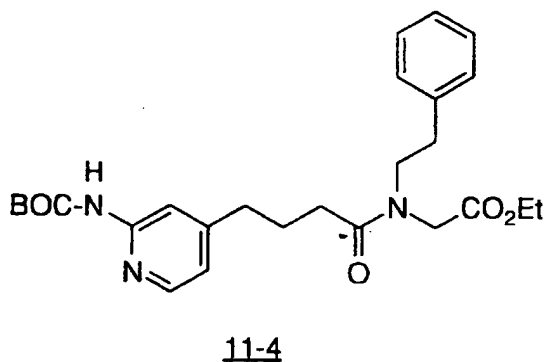
- 106 -

SCHEME 11 CONTINUED

- 107 -

N-(2-Phenethyl)glycine ethyl ester (11-3)

- A solution of amine 11-1 (20.0 g, 165 mmol), NEt₃ (47 ml, 330 mmol) in CH₂Cl₂ at 0°C was treated with bromide 11-2 (22.4 ml, 182 mmol) followed by the removal of the cooling bath. After 1.0 h, the solution was washed with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 50% EtOAc/hexanes) afforded ester 11-3 as a yellow oil.
- 10 TLC R_f 0.25 (silica, 50% EtOAc/hexanes)
¹H NMR (400 MHz, CD₃OD) 7.25 (m, 5H), 4.15 (q, J = 7 Hz, 2H), 3.37 (s, 2H), 2.81 (m, 4H), 1.23 (t, J = 7 Hz, 3H).



- 15 [4-(2-Boc-aminopyridin-4-yl)butanoyl]-N-(2-phenethyl)glycine ethyl ester (11-4)

A solution of acid 4-1 (1.5 g, 5.35 mmol), amine 11-3 (1.66 g, 8.03 mmol), BOP reagent (2.61 g, 5.89 mmol), NMM (3.0 ml, 21.4 mmol) and CH₃CN (30 ml) was stirred at ambient temperature for

- 108 -

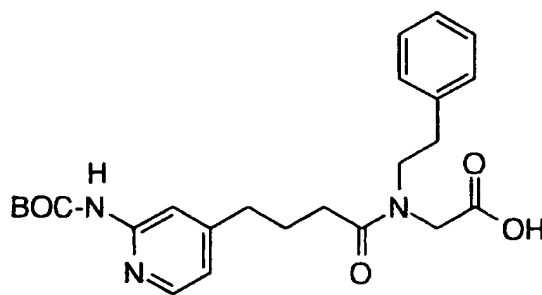
18 h. The solution was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄, brine, dried (MgSO₄) and concentrated.

Flash chromatography (silica, 50% EtOAc/hexanes 80%

EtOAc/hexanes) furnished ester 11-4 as a yellow solid.

5 TLC R_f 0.35 (silica, 50% EtOAc/hexanes)

¹H NMR (400 MHz, CDCl₃) δ 8.12 (d, J = 5 Hz, 1H), 7.77 (m, 2H), 7.21 (m, 4H), 7.10 (d, J = 7 Hz, 1H), 6.79 (m, 1H), 4.18 (q, J = 7 Hz, 2H), 4.02 (s, 2H), 3.58 (m, 2H), 2.82 (m, 2H), 2.62 (t, J = 7 Hz, 0.64 H), 2.57 (t, J = 7 Hz, 1.36 H), 2.15 (m, 2H), 1.91 (m, 2H), 1.52 (s, 9H),
10 1.27 (m, 3H).



11-5

[4-(2-BOC-Aminopyridin-4-yl)butanoyl]-N-(2-phenethyl)glycine (11-5)

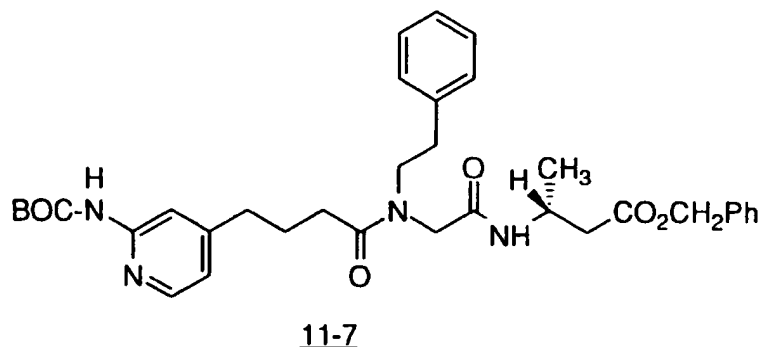
15 A solution of ester 11-4 (1.8 g, 3.84 mmol), 1N NaOH (6 ml, 6 mmol) and EtOH (10 ml) was stirred at ambient temperature for 30 minutes. The solution was acidified with 10% KHSO₄ and then extracted with EtOAc. The EtOAc phase was washed with brine, dried (MgSO₄) and concentrated to furnish acid 11-5 as a yellow solid.

20 TLC R_f 0.80 (silica, 20:1:1 CH₂Cl₂/MeOH/AcOH)

¹H NMR (400 MHz, CD₃OD) δ 8.12 (m, 1H), 7.17-7.29 (m, 7H), 4.06 (m, 2H), 3.61 (t, J = 7 Hz, 2H), 2.85 (t, J = 7 Hz, 2H), 2.81 (m, 0.64 H), 2.63 (t, J = 8 Hz, 1.36 H), 2.35 (t, J = 7 Hz, 0.64 H), 2.14 (t, J = 7 Hz, 1.36 H), 1.79 (m, 2H), 1.57 (s, 9H).

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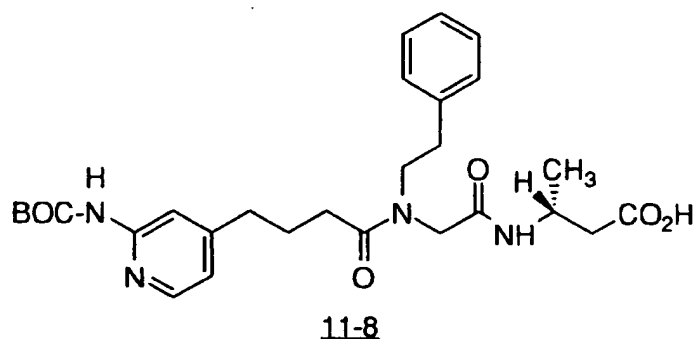
- 109 -



4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine benzyl ester (11-7)

- 5 A solution of acid 11-5 (400 mg, 0.91 mmol), amine 11-6 (available from Celgene) (285 mg, 1.09 mmol), BOP reagent (440 mg, 0.997 mmol), NMM (502 μ l, 3.63 mmol) and CH₃CN (20 ml) was stirred at ambient temperature for 18 h. The solution was diluted with EtOAc and then washed with H₂O, sat. NaHCO₃, 10% KHSO₄, brine,
- 10 dried (MgSO₄) and then concentrated. Flash chromatography (silica, 80% EtOAc/hexanes) furnished benzyl ester 11-7 as a yellow oil. TLC R_f 0.49 (silica, EtOAc)
- 15 ¹H NMR (400 MHz, CD₃OD) δ 8.06 (d, J = 5 Hz, 1H), 7.7 (s, 0.32 H), 7.68 (s, 0.68 H), 7.09-7.36 (m, 10 H), 6.83 (m, 1H), 5.16 (s, 1.36 H), 5.08 (s, 0.64 H), 4.29 (m, 1H), 3.93 (m, 2H), 3.51 (t, J = 7 Hz, 2H), 2.79 (q, J = 7 Hz, 2H), 2.50-2.61 (m, 4H), 2.25 (t, J = 8 Hz, 0.64 H), 2.09 (t, J = 7 Hz, 1.36 H), 1.73-1.84 (m, 4H), 1.51 (s, 9H), 1.25 (d, J = 7 Hz, 3H).

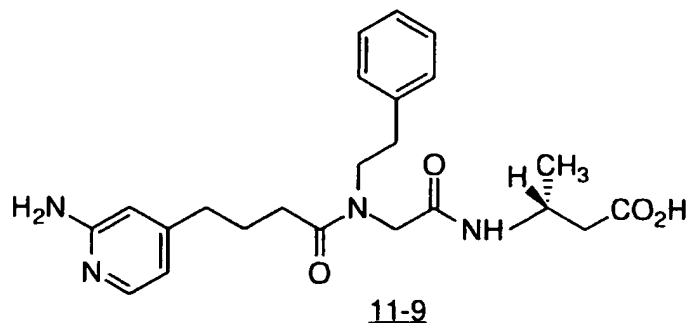
- 110 -



4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine (11-8)

- 5 A solution of benzyl ester 11-7 (380 mg, 0.597 mmol), 1N NaOH (1 ml, 1.0 mmol) and EtOH (5 ml) was stirred at ambient temperature for 1.0 h. The solution was acidified with 10% KHSO₄ and then extracted with EtOAc. The EtOAc phase was washed with brine, dried (MgSO₄) and concentrated to furnish acid 11-8 as a yellow oil.
- 10 ¹H NMR (400 MHz, CD₃OD) δ 8.13 (m, 1H), 7.15-7.35 (m, 7H), 4.24 (m, 1H), 3.91 (m, 2H), 3.58 (m, 2H), 2.81 (m, 2.64 H), 2.62 (t, J = 8 Hz, 1.36 H), 2.36 (t, J = 7 Hz, 0.64 H), 2.14 (t, J = 7 Hz, 1.36 H), 1.79 (m, 2H), 1.57 (s, 9H), 1.19 (m, 3H).

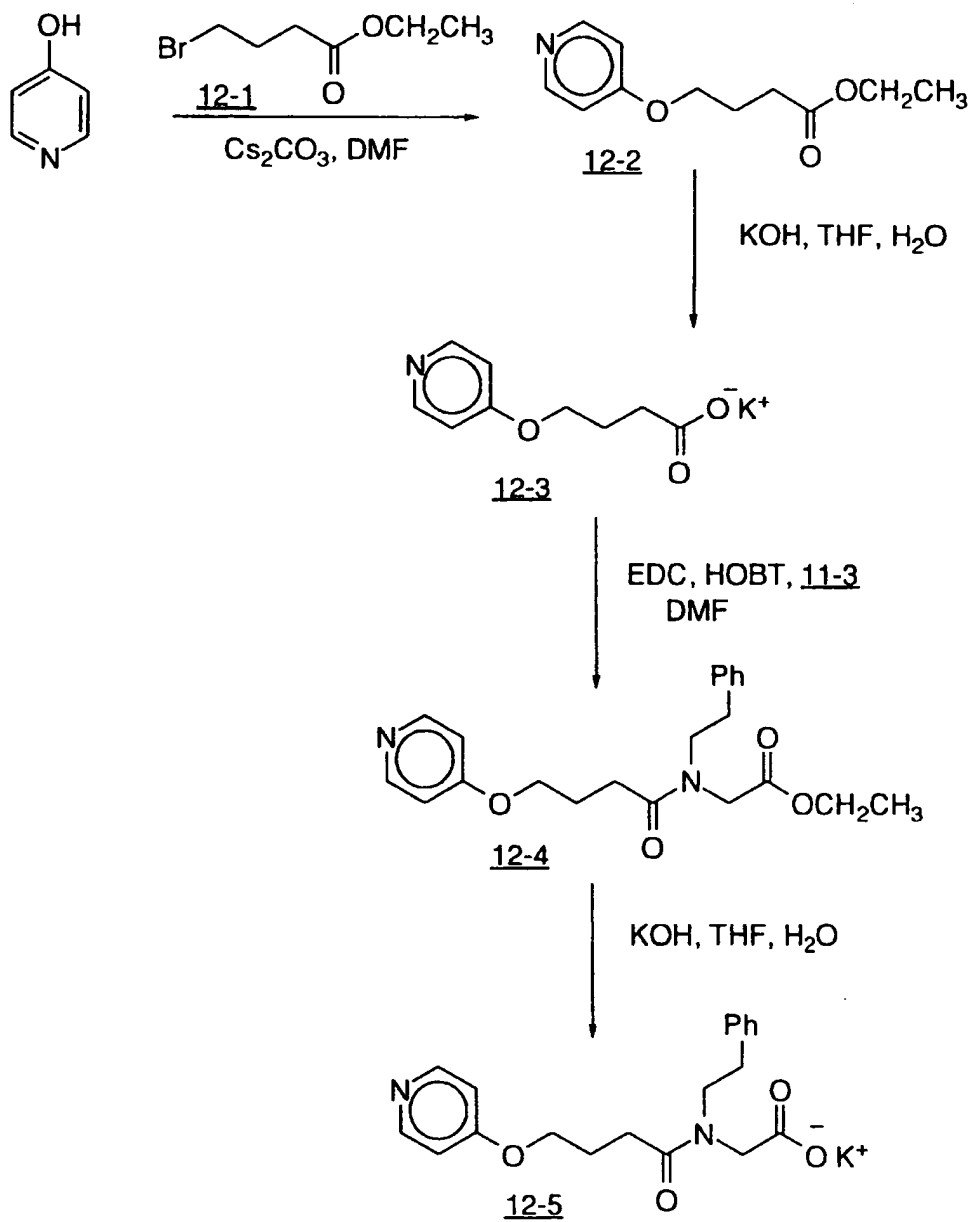
- 111 -



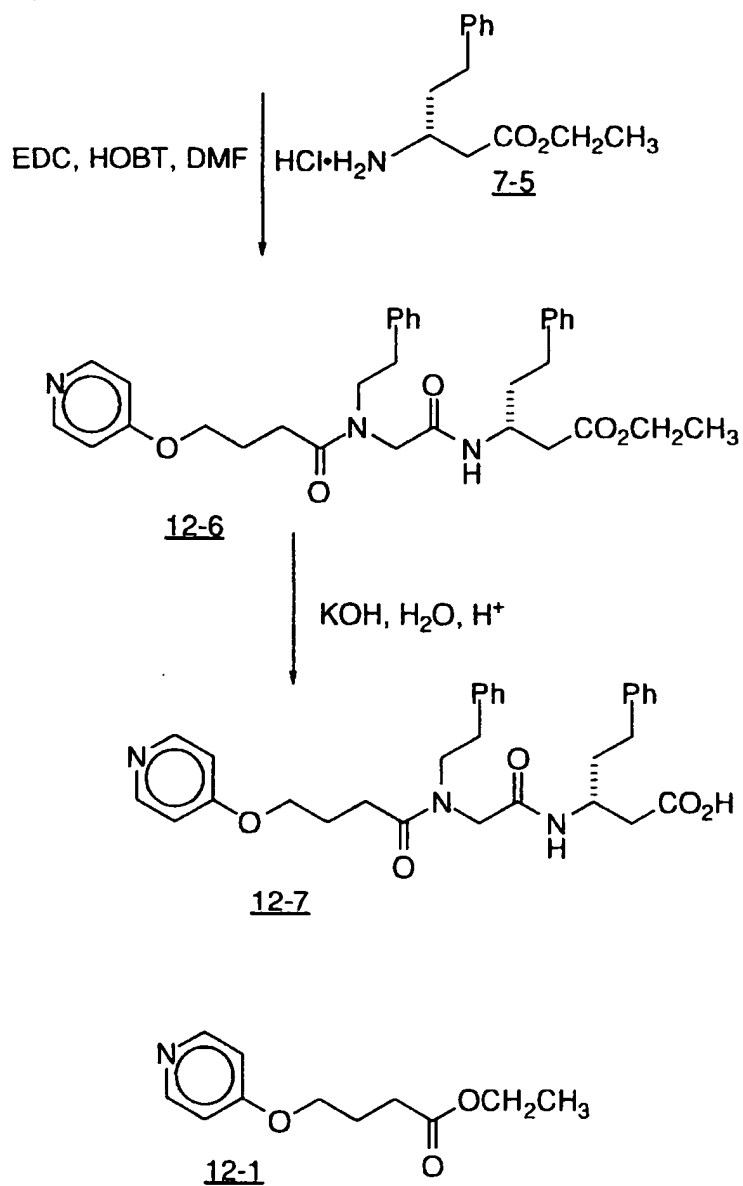
4-(2-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine (11-9)

- 5 A solution of acid 11-8 (320 mg, 0.59 mmol) in CH_2Cl_2 (5 ml) was treated with TFA (5 ml). After 1.0 h, the solution was concentrated and then azeotroped with toluene. Flash chromatography (silica, 10:10:1:1 EtOAc/EtOH/ NH_4OH / H_2O) furnished amine 11-10 (210 mg) as a white solid.
- 10 TLC R_f = 0.28 (silica, 5:5:5:5 EtOAc/EtOH/ NH_4OH / H_2O)
 ^1H NMR (400 MHz, CD_3ODD) δ 7.71 (d, J = 6 Hz, 1H), 7.15-7.32 (m, 5H), 6.62-6.69 (m, 2H), 4.25 (m, 1H), 3.99 (m, 2H), 3.58 (t, J = 7 Hz, 2H), 2.81 (m, 2H), 2.61 (t, J = 7 Hz, 0.64 H), 2.31-2.51 (m, 3.36 H), 2.12 (td, J = 3 Hz, 7 Hz, 1.36 H), 1.89 (t, J = 8 Hz, 0.64 H), 1.79 (m,
- 15 2H), 1.19 (m, 3H).

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SCHEME 12

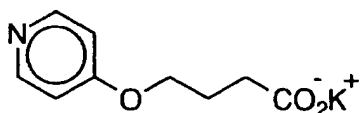
- 113 -

SCHEME 12 CONTINUED

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Ethyl-4-(4-Pyridyloxy)butyrate (12-2)

- A mixture of 4-hydroxypyridine (10 g, 105 mmol), ethyl 4-bromobutyrate 12-1 (15.0 ml, 105 mmol) and Cs₂CO₃ (34.2 g, 105 mmol) in DMF (100 ml) was stirred at room temperature for 24 h. The reaction was filtered and the filtrate diluted with ethyl acetate (300 ml) and washed with water (4 x 100 ml) and brine (100 ml) then dried (Na₂SO₄), filtered, and evaporated. The resulting oil was purified by chromatography on silica gel (3% CH₃OH/CH₂Cl₂) to give 12-2 as a colorless glass.
- 10 TLC R_f 0.45 (silica, 5% CH₃OH/CH₂Cl₂)
¹H NMR (300 MHz, CDCl₃) δ 8.41 (d, J=6.8Hz, 2H), 6.83 (d, J=6Hz, 2H), 4.16 (q, J=7Hz, 2H), 4.07 (t, J=7Hz, 2H), 2.52 (t, J=7Hz, 2H), 2.81 (t, J=7Hz, 2H), 1.23 (t, J=7.0Hz, 3H).



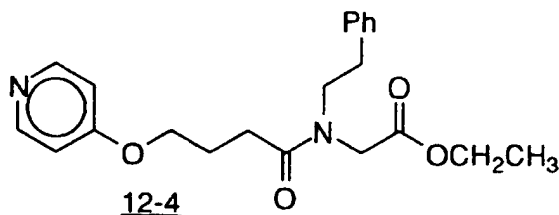
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12-3Potassium 4-(4-pyridyloxy)butyrate (12-3)

- The ester 12-1 (2.5 g, 12.0 mmol) was dissolved in 10 ml THF and treated with 0.5 N KOH (24 ml, 12.0 mmol) and H₂O (10 ml). The resulting solution was stirred at room temperature for 78 h then evaporated at reduced pressure to give 12-2 as a white solid.
- 20 ¹H NMR (300 MHz, D₂O) δ 8.19 (d, J = 6.8 Hz, 2H), 6.83 (d, J = 6.8 Hz, 2H), 6.83 (d, J = 6.8 Hz, 2H), 3.96 (t, J = 7.1 Hz, 2H), 2.18 (t, J = 7.1 Hz, 2H), 1.93 (m, 2H).

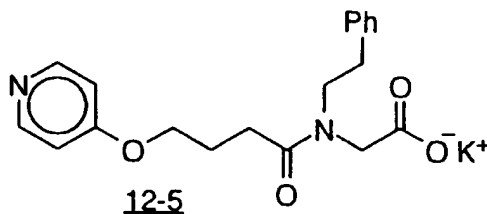
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4-(4-Pyridyloxy)butyrate-N-(2-phenethyl)glycine ethyl ester (12-4)

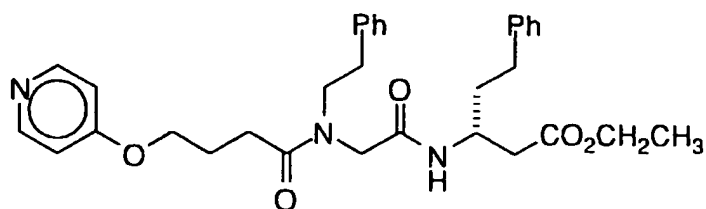
- The alkoxy pyridine 12-3 (298 mg, 1.36 mmol) and amine 11-3 (450 mg, 1.36 mmol) were combined with EDC (260 mg, 136 mmol), HOBT (208 mg, 136 mmol), in DMF (30 ml) and stirred at room temperature for 16 h. The solution was then diluted with ethyl acetate (200 ml) and washed with sat. NaHCO₃ (2 x 100 ml) and brine (100 ml). The organic layer was dried (Na₂SO₄), filtered, and evaporated and the residue chromatographed on silica gel (3% CH₃OH/CH₂Cl₂) to give 12-4 as a colorless glass.
- ¹H NMR (300 MHz, CDCl₃) δ 8.41 (d, J = 6.5 Hz, 2H), 7.25 (m, 5H), 6.78 (d, J = 6.5 Hz, 2H), 61.23 (m, 2H), 4.02 (s, 2H), 4.00 (m, 2H), 3.63 (m, 2H), 3.41 (m, 2H), 2.15 (m, 2H), 1.31 (m, 3H).



4-(4-Pyridyloxy)butyrate-N-(2-phenethyl)glycine potassium salt (12-5)

- Ester 12-4 (360 mg, 0.97 mmol) was hydrolyzed in 0.5 N KOH (1.94 ml, 0.97 mmol) to give the potassium salt 12-5 as a white solid.
- ¹H NMR (300 MHz, DMSO-d₆) δ 8.38 (d, J = 6.5 Hz, 2H), 7.25 (m, 5H), 6.93 (d, J = 6.5 Hz, 2H), 4.016 (m, 2H), 3.45 (m, 2H), 3.25 (s, 2H), 2.68 (m, 2H), 2.21 (m, 2H), 1.86 (m, 2H).

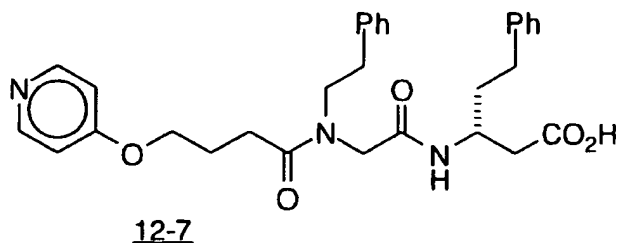
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12-6

4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine ethyl ester (12-6)

- Acid salt 12-5 (352 mg, 0.93 mmol) and amino ester 7-5 (240 mg, 0.93 mmol), HOBt (142 mg, 0.93 mmol), EDC (198 mg, 0.93 mmol), and triethylamine (130 μ l, 0.93 mmol) was dissolved in DMF (15 ml) and stirred at room temperature for 18 h. The solution was diluted with ethyl acetate (200 ml) washed with sat. NaHCO_3 , water and brine (100 ml each), dried (Na_2SO_4) and concentrated to give a colorless oil. Chromatography on silica gel afforded 12-6 as a colorless glass.
- TLC R_f 0.50 (silica, 3% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$)
- ^1H NMR (300 MHz, CDCl_3) δ 8.40 (d, $J = 6.6$ Hz, 2H), 7.25 (m, 10H), 6.85 (t, $J = 7.4$ Hz, 1H), 7.25 (d, $J = 6.6$ Hz, 2H), 4.25 (m, 1H), 4.18 (m, 2H), 4.00 (m, 2H), 3.60 (m, 2H), 2.95 (m, 2H), 2.63 (m, 2H), 2.58 (m, 2H), 2.40 (m, 2H), 2.08 (m, 2H), 1.85 (m, 2H), 1.16 (m, 3H).

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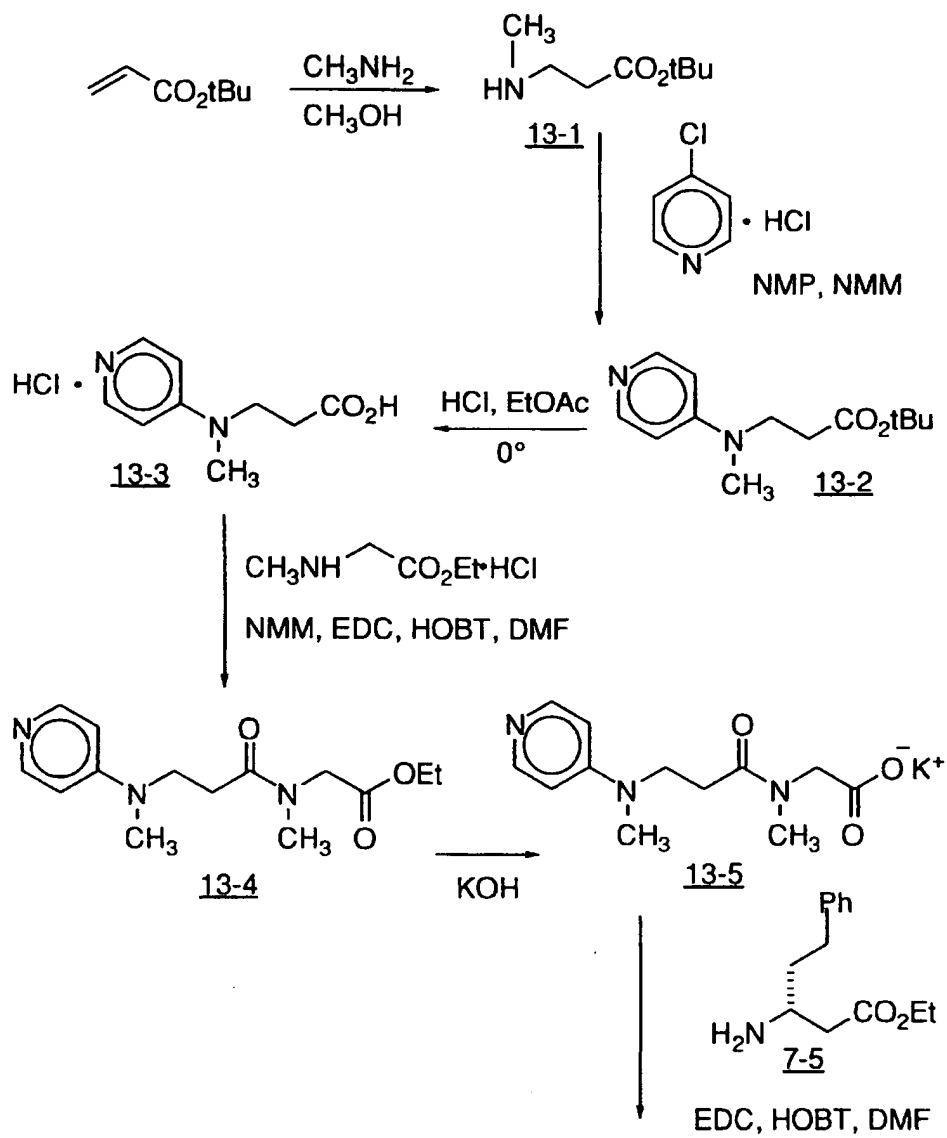


4-(4-Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine (12-7)

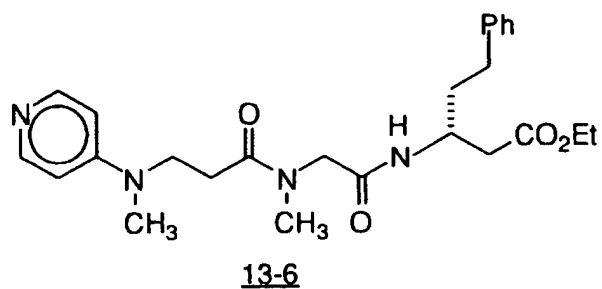
5 Ester 12-6 (123 mg, 0.23 mmol) was hydrolyzed with 0.5 N KOH and the acid was isolated as its TFA salt following preparative reverse phase chromatography.

10 ¹H NMR (300 MHz, CD₃OD) δ 8.63 (d, J = 6.5 Hz, 2H), 7.52 (d, J = 6.5 Hz, 2H), 7.20 (m, 10H), 4.41 (m, 1H), 4.32 (m, 2H), 4.01 (m, 2H), 3.81 (m, 2H), 2.85 (m, 2H), 2.63 (m, 2H), 2.30 (m, 2H), 2.41 (m, 2H), 2.20 (m, 2H), 1.85 (m, 2H).

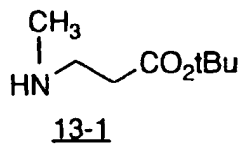
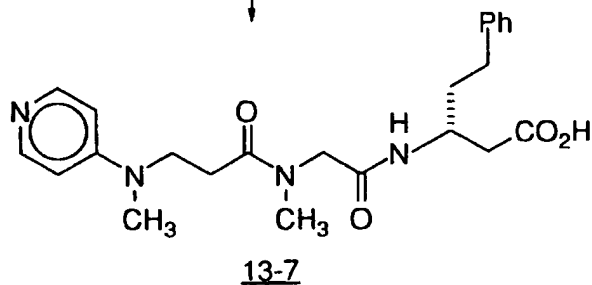
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SCHEME 13

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SCHEME 13 CONTINUED

KOH



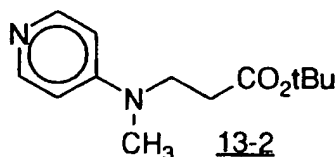
5

tert-Butyl 3-N-methylaminopropionate (13-1)

Tert-butyl acrylate (15 g, 117 mmol) was added to a solution of methanol saturated with CH₃NH₂ (300 ml) and stirred at room temperature for 16 h. The solution was evaporated to afford 13-1 as a colorless liquid.

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^1H NMR (300 MHz, CDCl_3) δ 2.81 (t, $J = 7.2$ Hz, 2H), 2.43 (t, $J = 7.2$ Hz, 2H), 1.45 (s, 9H).



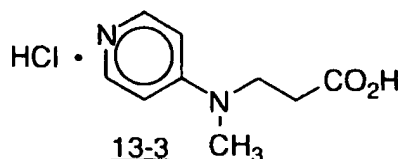
5

tert-Butyl 3-[(N-methyl-N-(4-pyridyl)]aminopropionate (13-2)

A mixture of 4-chloropyridine hydrochloride (10 g, 75 mmol), 13-1 (12 g, 75 mmol) and N-methylmorpholine (9.1 ml, 82.5 mmol) in N-methyl pyrrolidinone (100 ml) was heated at 120°C for 16 h. The solvent was removed at reduced pressure and the residue partitioned between EtOAc (100 ml) and water (50 ml). The organic layer was washed with water and brine (50 ml each) then dried (Na_2SO_4), filtered and evaporated. The ester 13-2 was isolated as a colorless glass following flash chromatography on silica gel (5% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$).

^1H NMR (300 MHz, CDCl_3) δ 8.30 (d, $J = 6.8$ Hz, 2H), 6.91 (d, $J = 6.8$ Hz, 2H), 3.81 (t, $J = 7.1$ Hz, 3H), 3.22 (s, 3H), 2.65 (t, $J = 7.1$ Hz, 2H), 1.41 (s, 9H).

20

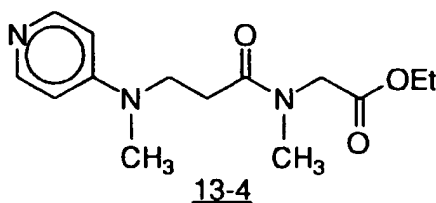


3-[(N-Methyl-N'-(4-pyridyl)]aminopropionate hydrochloride (13-3)

A solution of 13-2 (2.2 g, 9.3 mmol) in 75 ml anhydrous EtOAc was cooled to 0° and treated with HCl gas for 10 min. The solution was warmed to room temperature and stirred. For 16 h the resulting solid was filtered to give 13-3 as a hygroscopic yellow solid.

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^1H NMR (300 MHz, DMSO- d_6) δ 8.26 (d, J = 6.8 Hz, 2H), 7.0 (br d, 2H), 3.82 (t, J = 7.1 Hz, 2H), 3.21 (s, 3H), 2.60 (t, J = 7.1 Hz, 2H).



5

3-[(N-methyl-N-(4-pyridyl)]aminopropionyl-sarcosine ethyl ester (13-4)

Acid 13-3 (383 mg, 1.5 mmol) was coupled with sarcosine ethyl ester hydrochloride (253 mg, 1.65 mmol) following the EDC/HOBT procedure previously described to give 13-4 as a colorless glass.

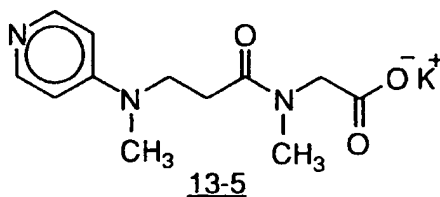
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TLC R_f 0.45 (silica, 3% $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$)

^1H NMR (300 MHz, CDCl_3) δ 8.21 (d, J = 6.8 Hz, 2H), 6.51 (d, J = 6.8 Hz, 2H), 4.20 (q, J = 7.0 Hz, 2H), 4.18 (s, 2H), 3.75 (t, J = 7.0 Hz, 2H), 3.09 (s, 3H), 3.04 (s, 3H), 2.65 (t, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz,

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3H).

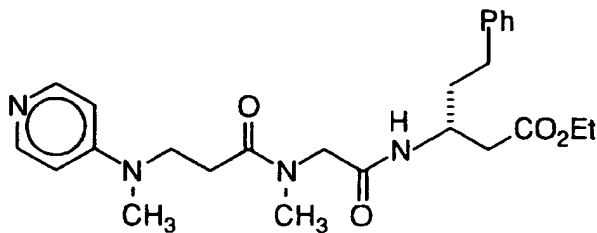


20 3-[(N-Methyl)-N'-(4-pyridyl)]aminopropionyl-sarcosine potassium salt (13-5)

A solution of 13-4 (353 mg, 1.26 mmol) in THF (5 ml) was treated with 0.5 N KOH (2.52 ml, 1.21 mmol) and H_2O (5 ml) and stirred at room temperature for 18 h. The solvent was removed *in vacuo* to afford the potassium salt 13-5 as a white solid.

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¹H NMR (300 MHz, DMSO-d₆) δ 8.08 (d, J = 6.7 Hz, 2H), 6.57 (d, J = 6.7 Hz, 2H), 3.61 (t, J = 7 Hz, 2H), 3.51 (s, 2H), 2.86 (s, 3H), 2.75 (s, 3H), 2.42 (t, J = 7.0 Hz, 2H).

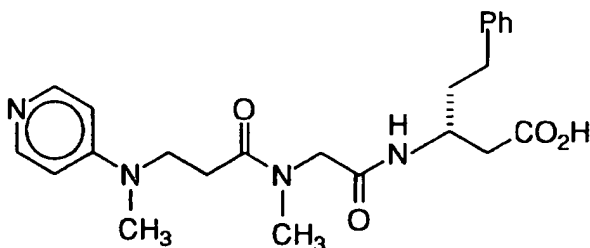
13-6

5

3-[(N-Methyl)-N'-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)-β-alanine ethyl ester (13-6)

- The acid 13-5 was coupled with 7-5 (229 mg, 0.88 mmol) under the EDC/HOBT procedure to afford 13-6 following chromatography (CH₂Cl₂/CH₃OH/NH₂/OH, 90:8:2)
- ¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, J = 6.8 Hz, 2H) 7.25 (m, 2H), 6.73 (d, J = 7.0 Hz, 1H), 6.51 (d, J = 6.8 Hz, 2H), 4.36 (m, 1H), 61.18 (m, 2H), 3.89 (m, 2H), 3.81 (t, J = 7.0 Hz, 2H), 3.06 (s, 3H), 2.98 (s, 3H), 2.85 (m, 2H), 2.65 (m, 2H), 2.51 (m, 2H), 1.83 (m, 2H), 1.20 (m, 3H).
- 10
- 15

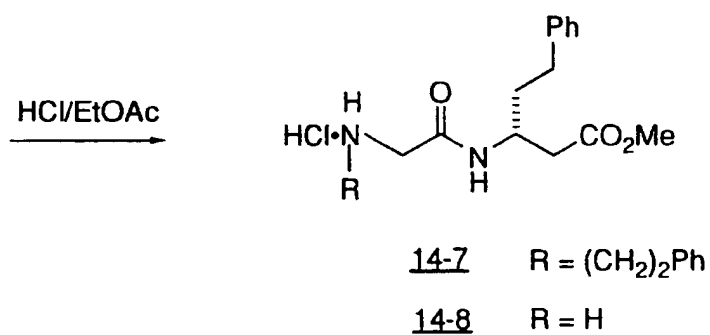
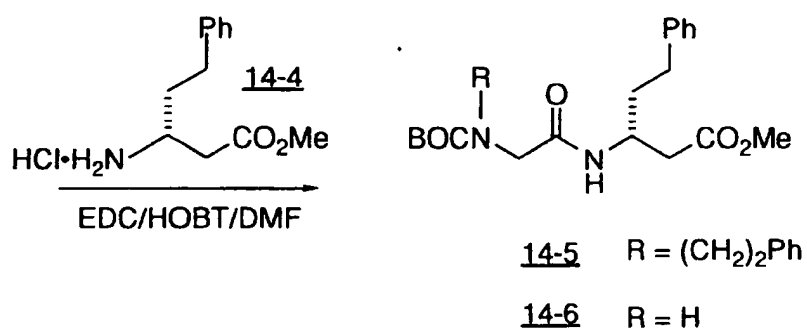
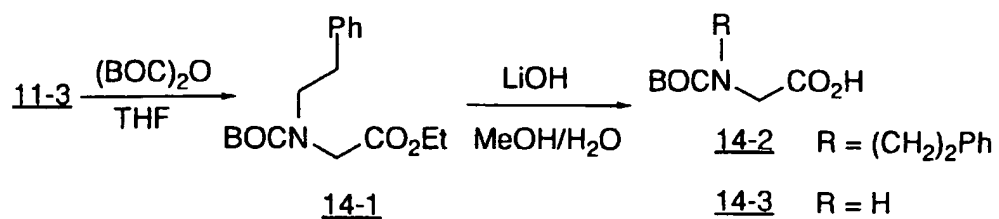
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13-7

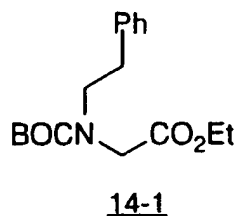
3-[(N-Methyl)-N'-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)-β-alanine (13-7)

- 5 A solution of the ester 13-6 (75 mg, 0.16 mmol) in THF (5 ml) was treated with 0.5N KOH (320 ml, 0.16 mmol) and H₂O (5 ml). The resulting solution was stirred at room temperature for 7.5 h then evaporated at reduced pressure. The resulting residue was purified by reverse phase a white powder.
- 10 ¹H NMR (300 MHz, DMSO-d₆) δ 8.61 (d, J = 6.8 Hz, 2H), 7.25 (m, 5H), 7.18 (d, J = 7.0 Hz, 1H), 6.83 (d, J = 6.8 Hz, 2H), 4.35 (m, 1H), 3.83 (m, 2H), 3.81 (t, 2H), 3.13 (s, 2H), 2.95 (s, 3H), 2.85 (m, 2H), 2.65 (m, 2H), 2.56 (m, 2H), 1.86 (m, 2H).

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SCHEME 14

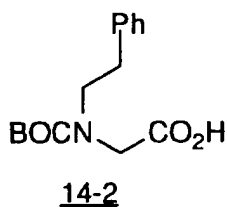
- 125 -



N-(t-Butoxycarbonyl)-N-(2-phenylethyl)glycine ethyl ester (14-1)

- 5 The amine 11-3 (1.11 g, 5.36 mmol) and (BOC)₂O (1.28 g, 5.9 mmol) in 10 ml THF were stirred for 48 h under argon. Removal of the solvent *in vacuo* gave a yellow oil which was purified by chromatography (silica, hexane/EtOAc 9:1) to afford 14-1 as a colorless oil.
- R_f (silica, hexane/EtOAc 9:1) 0.41.

10

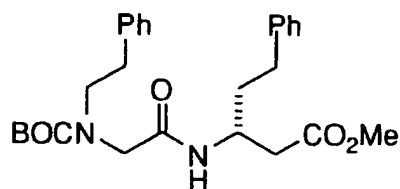


N-(t-Butoxycarbonyl)-N-(2-phenylethyl)glycine (14-2)

- 15 A solution of the ester 14-1 (1.7 g, 5.5 mmol), 11.1 mL 1N LiOH and 11 mL MeOH was stirred at room temperature for 16 h. The mixture was poured into water/EtOAc and acidified with 1N HCl to pH ≈ 3. After extraction with EtOAc (2x), the organic layers were washed with brine, dried (MgSO₄) and evaporated to give 14-2 as a foam which was used as such in the next step.

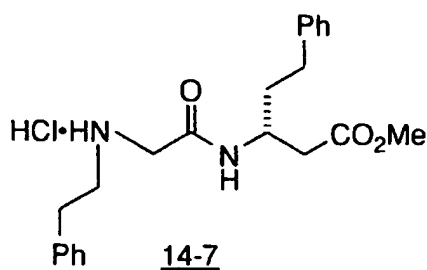
20

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14-5

N-[N-(t-Butoxycarbonyl)-N'-(2-phenylethyl)glycyl]-3(R)-(2-phenylethyl)-β-alanine methyl ester (14-5)

- 5 The acid 14-5 (502 mg, 1.8 mmol), 3(R)-(2-phenylethyl)-β-alanine methyl ester hydrochloride 14-4 (see U.S. Patent 5,281,585) (482 mg, 2.0 mmol), HOBt (267 mg, 2.0 mmol), EDC hydrochloride (515 mg, 2.7 mmol) and N-methylmorpholine (0.22 ml, 2.0 mmol) were stirred in 10 ml DMF for 16 h under argon. After pouring the
- 10 solution into EtOAc/10% citric acid (aqueous solution) the mixture was extracted twice with EtOAc, washed with water then brine, dried (MgSO₄) and the solvent removed *in vacuo*. The residual yellow oil was subjected to column chromatography (silica, hexane/EtOAc 1:1) to give 14-5 as a colorless oil.
- 15 R_f (silica, hexane/EtOAc 1:1) 0.44.

14-7

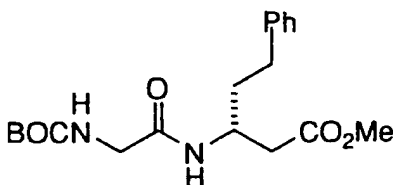
- 20 N-[N'-(2-phenylethyl)glycyl]-3(R)-(2-phenylethyl)-β-alanine methyl ester hydrochloride (14-7)

A solution of 14-5 (719 mg, 1.5 mmol) in 40 mL of EtOAc was treated with HCl (g) until saturated. After 30 min the solvent was

- 127 -

removed *in vacuo* and the residue was triturated with ether from which 14-10 crystallized as a white solid.

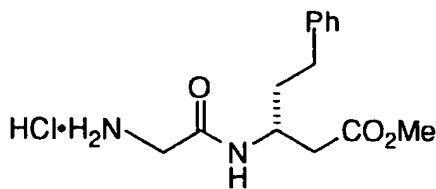
¹H NMR (CD₃OD) δ 1.87 (2H, m), 2.5-2.8 (4H, m), 3.05 (2H, m), 3.28 (2H, m), 3.62 (3H, s), 3.78 (1H, d), 3.84 (1H, d), 4.26 (1H, m), 7.1-7.4 (10H, m).

14-6

10 N-[N'-(t-Butoxycarbonyl)glycyl]-3(R)-(2-phenethyl)-β-alanine methyl ester (14-6)

N-(t-butoxycarbonyl)glycine 14-3 (Aldrich) was coupled with 14-4 according to the procedure described for the preparation of 14-5. The title compound 14-6 was purified by column chromatography (silica, hexane/EtOAc 1:1).

15 R_f (silica, hexane/EtOAc 1:1) 0.22.

14-8

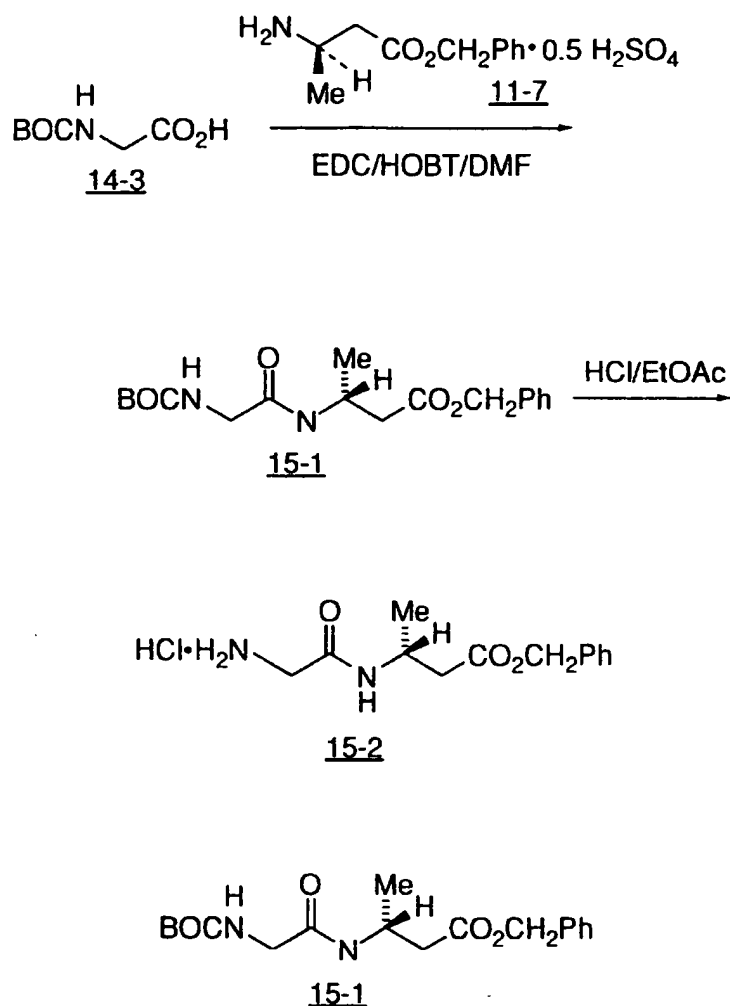
20 N-Glycyl-3(R)-(2-phenethyl)-β-alanine methyl ester hydrochloride (14-8)

Following the procedure described for the preparation of 14-7 compound 14-6 was converted into 14-8.

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^1H NMR (CD_3OD) δ 1.88 (2H, m), 2.5-2.8 (4H, m), 3.64 (5H, s), 4.25 (1H, m), 7.1-7.3 (5H, m).

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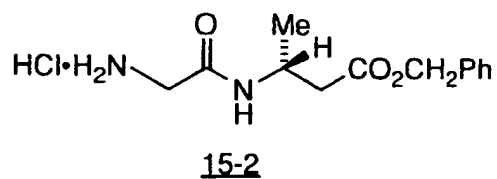
SCHEME 15

5

N-[N'-(t-Butoxycarbonyl)glycyl]-3(R)-methyl-β-alanine benzyl ester
(15-1)

- 10 N-(t-Butoxycarbonyl)glycine 14-3 (Aldrich) was coupled with 3(R)-methyl-β-alanine benzyl ester 0.5 H₂SO₄ 11-7 (Celgene) according to the procedure described for the preparation of 14-5. The title product 15-1 was then obtained by chromatography (silica, hexane/EtOAc 2:3).
R_f (silica, hexane/EtOAc 1:1) 0.3.

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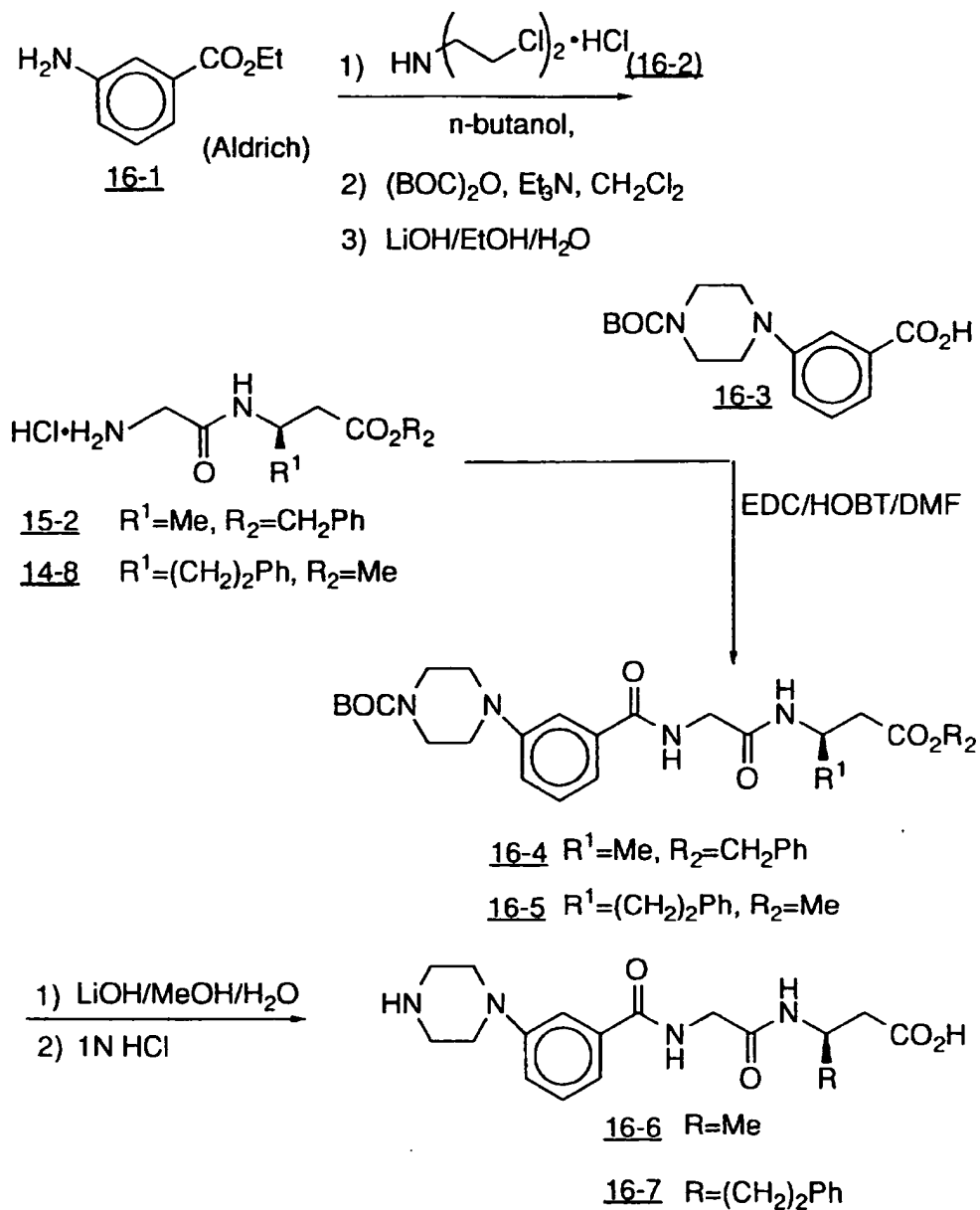
N-(Glycyl-3(R)-methyl-β-alanine benzyl ester hydrochloride (15-2)

5 Following the procedure for the preparation of 14-7, compound 15-1 was converted into 15-2 which was isolated as a white solid.

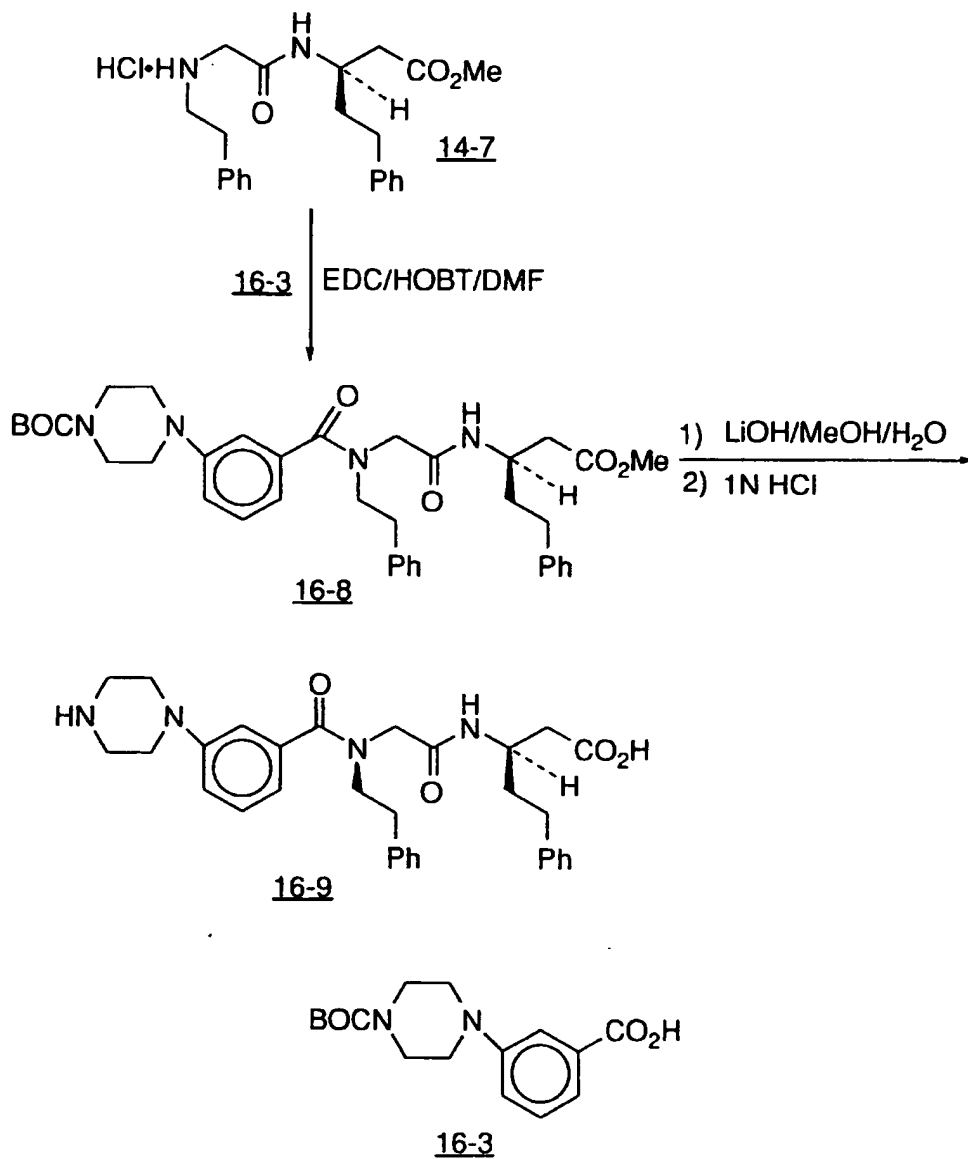
¹H NMR (CD₃OD) δ 1.22 (3H, d), 2.58 (2H, m), 3.53 (1H, d), 3.63 (1H, d), 6.3 (2H, s), 7.35 (5H, m).

10

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SCHEME 16

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SCHEME 16 CONTINUED

5

3-(4-(4-(tert-butoxycarbonyl)-1-piperidinyl)benzoic acid (16-3)

Ethyl 3-aminobenzoate 16-1 (Aldrich, 24.3 g, 0.147 mol)
and bis (2-chloroethyl)amine hydrochloride 16-2 (Aldrich, 26.3 g,

- 133 -

0.147 mol) were heated at reflux in 500 mL n-butanol for 24 h. The solution was concentrated *in vacuo*, the residue was taken up in EtOAc and washed successively with saturated aqueous NaHCO₃ then brine. After drying (MgSO₄), the solvent was removed and the resulting black oil chromatographed (silica, EtOAc then EtOAc/MeOH 1:1 then MeOH) to give the corresponding piperazine derivative as a mixture of ethyl and butyl esters.

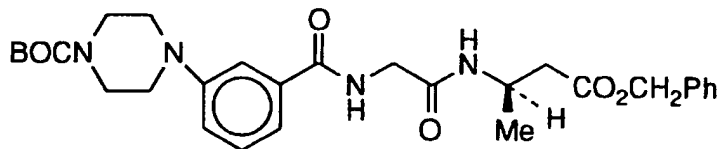
This piperazine (17.8 g, 76 mmol) was dissolved in 500 mL dry CH₂Cl₂ and Et₃N (13.3 ml, 95.6 mmol) was then added. To this cooled -5°C solution was added (BOC)₂O (17.4 g, 79.9 mmol) in 45 ml dry CH₂Cl₂ and stirring was continued until the reaction was complete (as monitored by TLC). The solution was poured into 10% citric acid solution then the organic layer was washed with water, saturated aqueous NaHCO₃ and brine. After drying over MgSO₄, the solvent was removed *in vacuo* to give a brown oil. Silica gel chromatography (hexane/EtOAc 1:1) gave the BOC-protected piperazine as a mixture of ethyl and butyl esters.

The BOC-protected piperazine (22.1 g) was dissolved in 150 ml 1N LiOH and 600 ml absolute ethanol and this solution was heated at reflux for 16 h. After removal of the ethanol, EtOAc and 10% citric acid solution were added. The organic layer was washed with 1N NaOH, the aqueous layer was then re-acidified with 1N HCl and extracted with EtOAc. This EtOAc extract was washed with brine, dried (MgSO₄) and concentrated to give 16-3 as a white solid.

R_f (silica, hexane/EtOAc 1:1) 0.22.

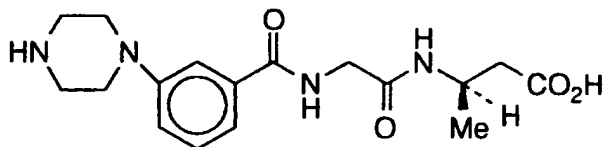
¹H NMR (CDCl₃) δ 1.49 (9H, s), 3.21 (4H, br t), 3.61 (4H, br t), 7.16 (1H, dd), 7.36 (1H, t), 7.64 (2H, m).

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16-4

N-{N'-3-(4-t-Butoxycarbonyl-1-piperiziny)benzoyl}glycyl-3(R)-methyl- β -alanine benzyl ester (16-4)

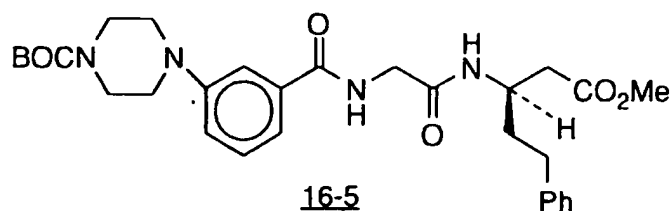
- The acid 16-3 was coupled with 15-2 according to the procedure described for the preparation of 14-5 to yield 16-4.
 5 R_f (silica, EtOAc) 0.45.

16-6

- 10 N-[N'-[3-(1-Piperaziny)benzoyl]glycyl]-3(R)-methyl- β -alanine trifluoroacetic acid salt (16-6)

- The ester 16-4 (452 mg, 0.84 mmol) was dissolved in 4 ml MeOH, treated with 1N LiOH (2.5 ml, 2.5 mmol) and stirred for 48 h. The solvent was removed under reduced pressure and to the residue was
 15 added 10 ml 1N HCl. After 10 min, the solution was concentrated and the residue purified by preparative HPLC (H₂O/CH₃CN with 0.1% TFA, gradient) to give 16-6.
 FAB mass spectrum m/z = 349 (m + 1)
¹H NMR (CD₃OD) δ 1.22 (3H, d), 2.43 (1H, dd), 2.57 (1H, dd), 3.38
 20 (4H, m), 3.46 (4H, m), 3.96 (1H, d), 4.04 (1H, d), 4.30 (1H, sextet), 7.25 (1H, m), 7.4 (2H, m), 7.5 (1H, m).

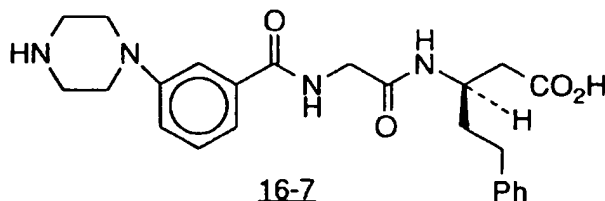
- 135 -



N-[N'-(3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl)glycyl]-3(R)-(2-phenethyl)-β-alanine methyl ester (16-5)

- 5 The acid 16-3 was coupled with 14-8 according to procedure described for the preparation 14-5 to yield 16-5.
¹H NMR (CDCl₃) δ 1.49 (9H, s), 1.90 (2H, m), 2.58 (2H, d), 2.63 (2H, m), 3.15 (6H, m), 3.55 (4H, m), 3.62 (3H, s), 4.10 (2H, d), 4.32 (1H, m), 7.0-7.5 (9H, m).

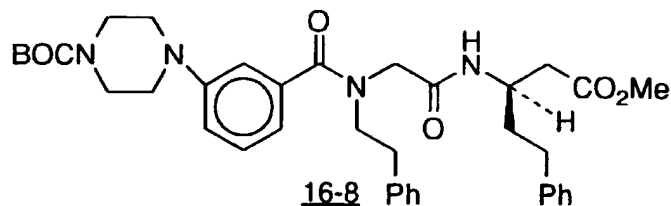
10



N-[N'-(1-Piperazinyl)benzoyl]glycyl]-3(R)-(2-phenethyl)-β-alanine trifluoroacetic acid salt (16-7)

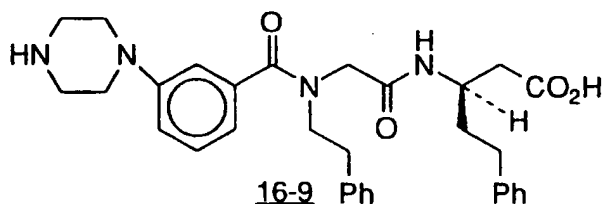
- 15 Following the procedure described for the preparation of 16-6, 16-5 was converted into 16-7.
 FAB mass spectrum m/z = 439 (m+1)
 Anal. calcd. for C₂₄ H₃₀ N₄ O₄ • 1.35 TFA • 1.0 H₂O
 C, 52.53; H, 5.51; N, 9.18
 20 found: C, 52.57; H, 5.44; N, 9.26

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N-[N'-(3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl)-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)-β-alanine methyl ester (16-8)

- 5 The acid 16-3 was coupled with 14-7 according to the procedure described for the preparation of 14-5 to yield 16-8.
R_f (silcia, EtOAc/hexane 2:1) 0.37.



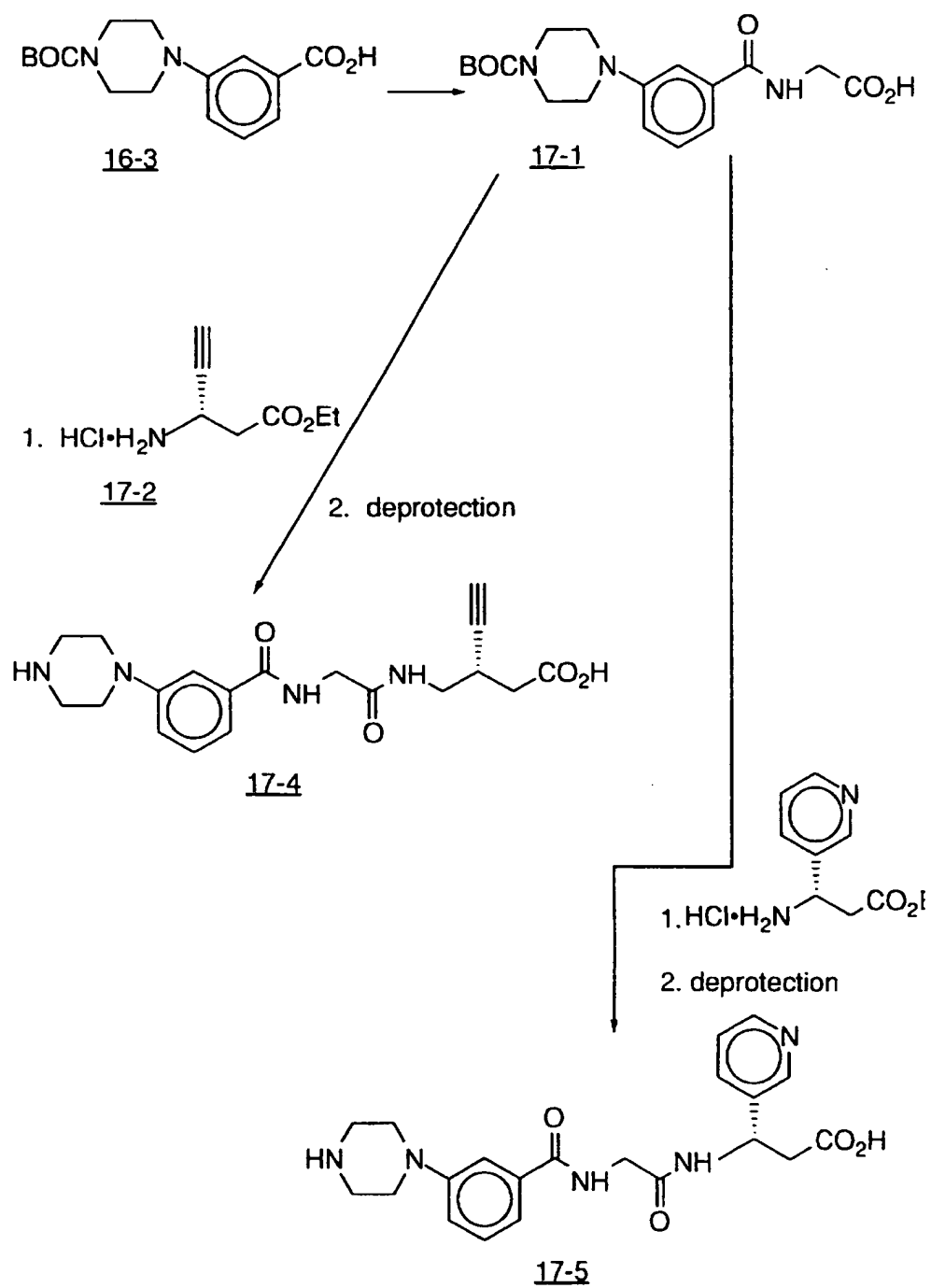
10

N-[N'-(3-(1-Piperazinyl)benzoyl)-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)-β-alanine trifluoroacetic acid salt (16-9)

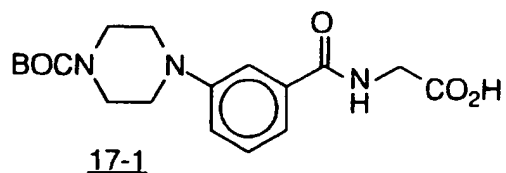
Following the procedure described for the preparation of 16-6, 16-8 was converted into 16-9.

- 15 FAB mass spectrum $m/z = 543 (m + 1)$
 Anal. calcd. for C₃₂ H₃₈ N₄ O₄ • 1.8 TFA • 0.8 H₂O
 C, 56.09; H, 5.47; N, 7.35
 found: C, 56.09; H, 5.41; N, 7.74

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SCHEME 17

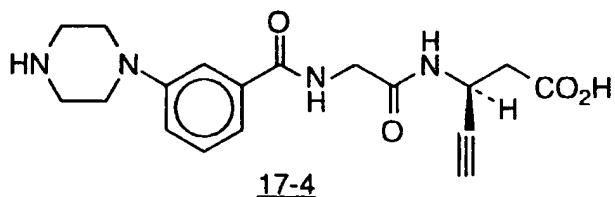
- 138 -



3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl glycine (17-1)

The acid 16-3 was coupled with glycine ethyl ester followed
 5 by hydrolysis of the resulting ester using previously described chemistry
 to yield 17-1.

¹H NMR (300 MHz, CD₃OD) δ 1.48 (9H, s), 3.22 (4H, m), 3.59 (4H,
 m), 4.08 (2H, s), 7.22 (1H, m), 7.40 (2H, m), 7.55 (1H, s).



N-[N'-(3-(1-piperazinyl)benzoyl)glycyl]-3(S)-ethynyl-β-alanine
 trifluoroacetic acid salt (17-4)

The acid 17-1 was coupled with 3(S)-ethynyl-β-alanine
 ethyl ester hydrochloride (Zablocki *et al.*, *J. Med. Chem.*, 1995, 38,
 15 2378-2394) using standard peptide coupling conditions. The product
 was then fully deprotected using previously described methodology to
 give, after reverse phase chromatography, 17-4 as the trifluoroacetate
 salt.

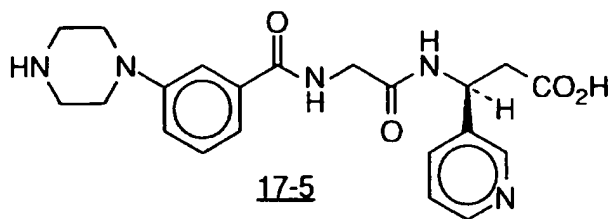
FAB mass spectrum m/z = 359 (M+1)

20 Anal. calculated for C₁₈H₂₂N₄O₄•1.10 TFA•0.30 H₂O

C, 49.59; H, 4.88; N, 11.45

Found: C, 49.58; H, 4.80; N, 11.57

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N-[N'-[3-(1-Piperazinyl)benzoyl]glycyl]-3(S)-(3-pyridyl)-β-alanine trifluoroacetic acid salt (17-5)

- 5 The acid 17-1 was coupled with 3(S)-(3-pyridyl)-β-alanine ethyl ester hydrochloride (Rico *et al.*, *J. Org Chem.*, 1993, vol. 58, p. 7948) using standard peptide coupling conditions. The product was then fully deprotected using previously described methodology to give, after reverse phase chromatography, 17-5 as the trifluoroacetate salt.

FAB mass spectrum $m/z = 412$ (M+1)

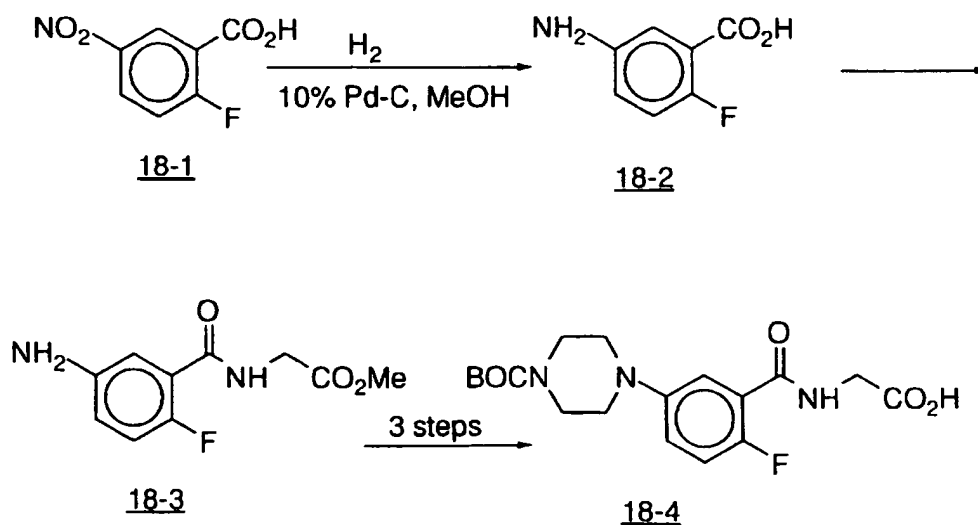
- 10 Anal. calculated for $C_{21}H_{25}N_5O_4 \cdot 2.55 \text{ TFA} \cdot 0.75 \text{ H}_2\text{O}$

C, 43.80; H, 4.09; N, 9.79

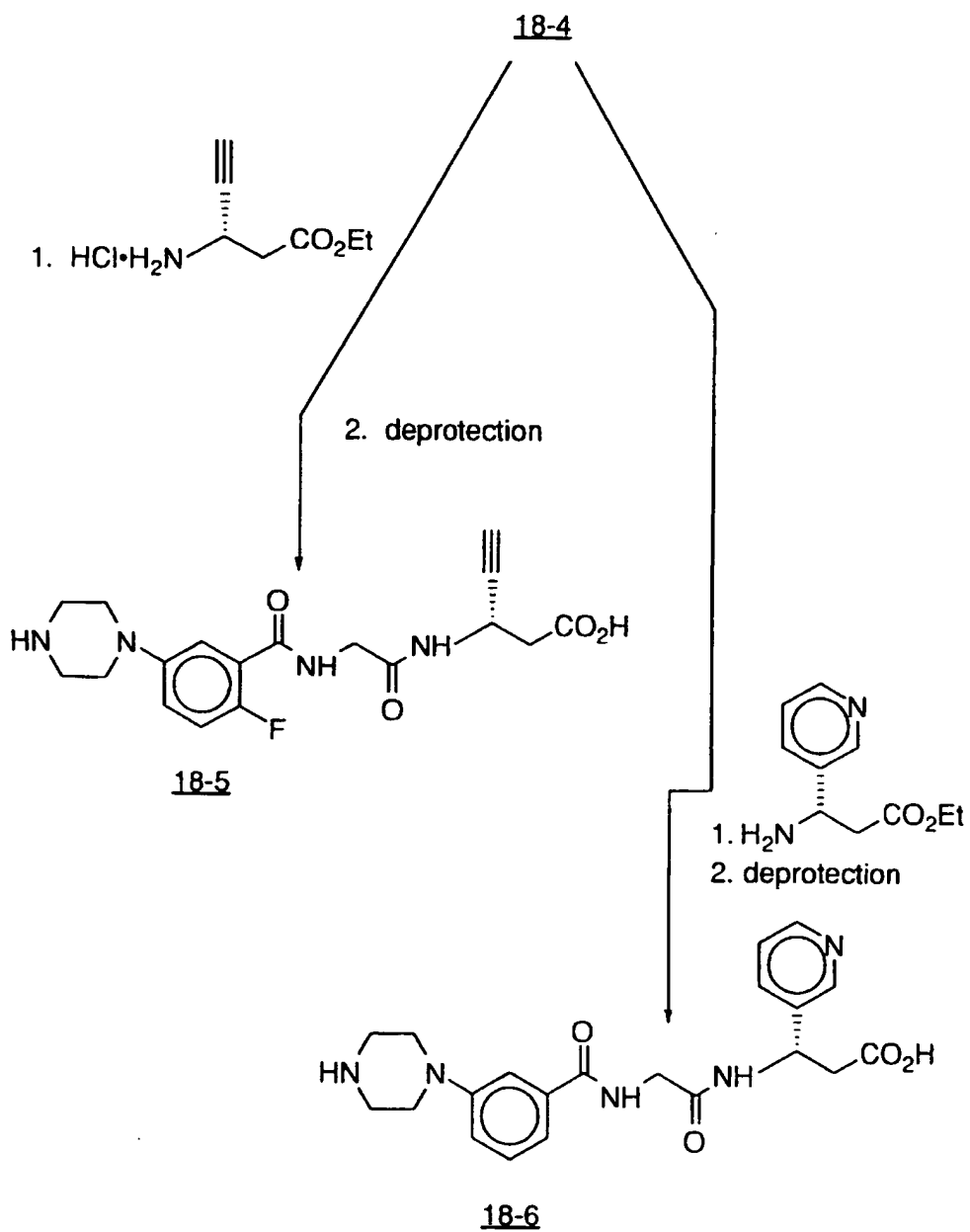
Found: C, 43.76; H, 3.98; N, 10.15

SCHEME 18

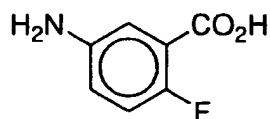
15



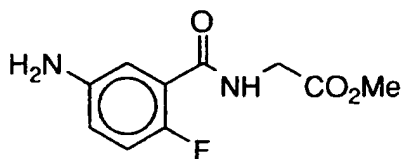
- 140 -

SCHEME 18 (CONT'D)

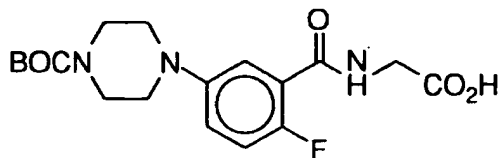
- 141 -

18-25-Amino-2-fluorobenzoic acid 18-2

- 2-Fluoro-5-nitrobenzoic acid 18-1 (Aldrich) was reduced using 10% Pd-C catalyst in MeOH under an atmosphere of H₂ to give, after filtration of the catalyst and removal of the solvent, 18-2 as a solid. R_f = 0.54 (silica, 10-1-1 EtOH•NH₄OH•H₂O)

18-3N-(5-Amino-2-Fluorobenzoyl)glycine methyl ester 18-3

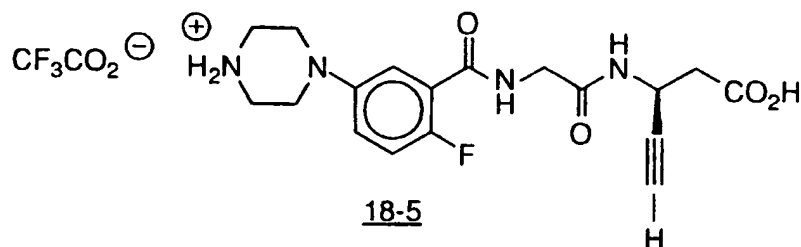
- The acid 18-2 was coupled with glycine methyl ester using standard peptide coupling conditions to give 18-3. R_f = 0.65 (silica; EtOAc/MeOH 9:1)

18-4

- 5-(4-t-Butoxycarbonyl-1-piperizinyl)-2-fluorobenzoyl glycine 18-4

Following the procedure described for the preparation of 16-3, the aniline 18-3 was converted into the piperazine-acid 18-4. ¹H NMR (300 MHz, CD₃OD) δ 1.46 (9H, s), 3.11 (4H, m), 3.58 (4H, m), 4.12 (2H, s), 7.05-7.21 (2H, m), 7.40 (1H, m).

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N-{N'-[2-Fluoro-5-(1-piperazinyl)benzoyl]glycyl}-3(S)-ethynyl- β -alanine trifluoroacetic acid salt 18-5

Following the procedure described for the preparation of

5 17-4, compound 18-4 was converted into 18-5.

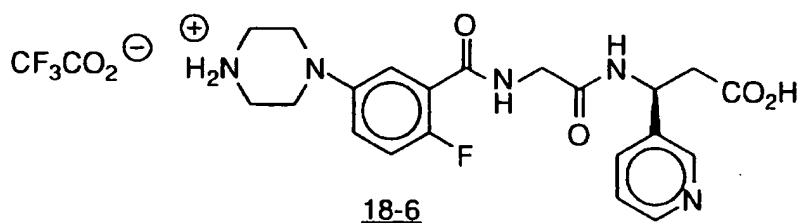
FAB mass spectrum m/z = 377 (M+1)

Anal. calculated for $C_{18}H_{21}N_4O_4F \cdot 1.30TFA \cdot 0.50 H_2O$

C, 46.37; H, 4.40; N, 10.50

Found: C, 46.34; H, 4.37; N, 10.58

10



N-{N'-[2-fluoro-5-(1-piperazinyl)benzoyl]glycyl}-3(S)-(3-pyridyl)- β -alanine trifluoroacetic acid salt 18-6

Following the procedure described for the preparation of

15 17-5, compound 18-4 was converted into 18-6.

FAB mass spectrum m/z = 430 (M+1)

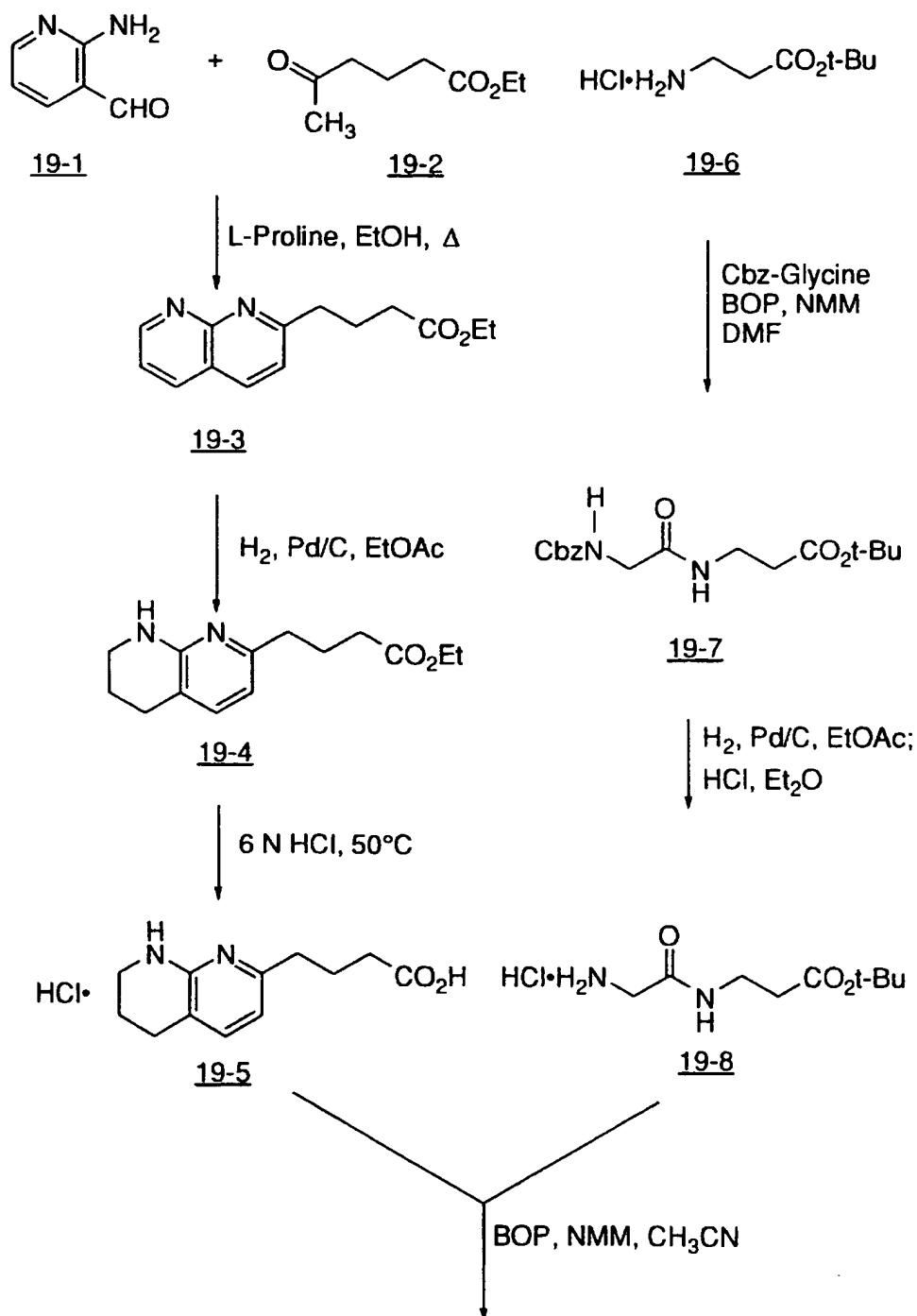
Analysis calculated for $C_{21}H_{24}N_5O_4F \cdot 2.65 TFA \cdot 0.90 H_2O$

C, 42.24; H, 3.83; N, 9.37

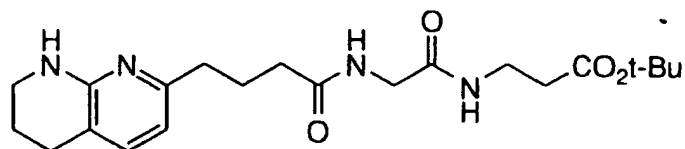
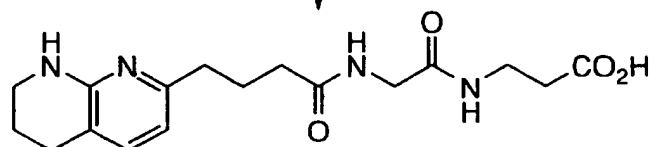
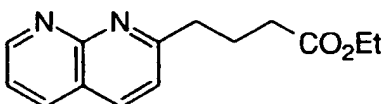
Found: C, 42.25; H, 3.81; N, 9.71

20

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SCHEME 19

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SCHEME 19 CONT'D19-9TFA, CH₂Cl₂19-1019-3

5

Ethyl 4-(1,8-naphthyridin-2-yl)butanoate (19-3)

Aminoaldehyde 19-1 (2.02 g, 16.6 mmol, prepared according to *Het.* 1993, 36, 2513), ketone 19-2 (5.3 mL, 33.1 mmol) and L-proline (0.48 g, 4.17 mmol) were combined in 75 mL EtOH.

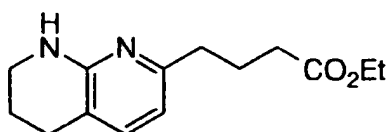
- 10 After heating at reflux overnight the reaction was concentrated. Flash chromatography (silica, EtOAc) provided 19-3 as an off-white crystalline solid.

TLC R_f 0.23 (silica, EtOAc)

- ¹H NMR (300 MHz, CDCl₃): δ 9.09 (dd, J=4, 2Hz, 1H), 8.17 (dd, J=8, 2Hz, 1H), 8.12 (d, J=8Hz, 1H), 7.46 (dd, J=8, 4Hz, 1H), 7.42 (d, J=8Hz,
- 15

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1H), 4.12 (q, J=7Hz, 2H), 3.11 (t, J=8Hz, 2H), 2.44 (t, J=7Hz, 1H), 2.26 (qn, J=8Hz, 2H), 1.25 (t, J=7Hz, 3H).

19-4

5

Ethyl 4-(1,2,3,4-tetrahydro-1,8-naphthyridin-7-yl)butanoate (19-4)

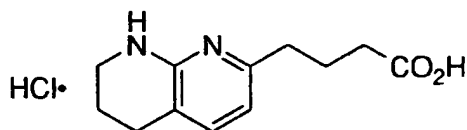
A solution of 19-3 (2.3 g, 9.4 mmol) in 50 mL EtOAc was treated with 10% Pd/C (230 mg) and a hydrogen balloon. After 4 d the reaction filtered through celite, concentrated, and purified by flash chromatography (silica, 70% EtOAc/hexane), providing 19-4 as a yellow oil.

10

TLC R_f 0.40 (silica, EtOAc)

¹H NMR (300 MHz, CDCl₃): δ 7.05 (d, J=7Hz, 1H), 6.35 (d, J=7Hz, 1H), 4.73 (br s, 1H), 4.12 (q, J=7Hz, 2H), 2.69 (t, J=6Hz, 2H), 2.57 (t, J=8Hz, 2H), 2.33 (t, J=7Hz, 2H), 1.98 (m, 2H), 1.90 (m, 2H), 1.25 (t, J=7Hz, 3H).

15

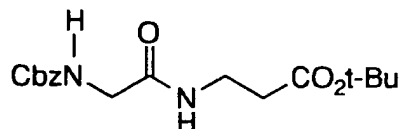
19-5

20 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoic acid hydrochloride (19-5)

Ester 19-4 (1.8 g, 7.25 mmol) in 36 mL 6 N HCl was heated at 50°C for 4 h, then concentrated, providing 19-5 as a yellow solid.

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¹H NMR (300 MHz, CD₃OD): δ 7.59 (d, J=7Hz, 1H), 6.63 (d, J=7Hz, 1H), 3.50 (t, J=5Hz, 2H), 2.82 (t, J=6Hz, 2H), 2.74 (t, J=8Hz, 2H), 2.38 (t, J=7Hz, 2H), 2.02-1.90 (m, 4H).



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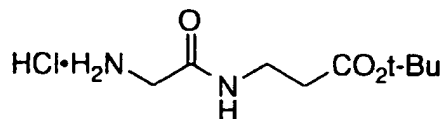
19-7

N-Cbz-Glycyl-β-alanine t-butyl ester (19-7)

N-CBz-Glycine (1.0 g, 4.78 mmol), amine 19-6 (0.91 g, 5.02 mmol), NMM (2.1 mL, 19.1 mmol) and BOP (3.17 g, 7.17 mmol) were combined in 15 mL DMF. After stirring overnight the mixture was concentrated, diluted with EtOAc, washed with water, sat. NaHCO₃, water, 5% KHSO₄ and brine, dried (MgSO₄), filtered and concentrated. Flash chromatography (silica, 60% EtOAc/hexane) provided 19-7 as a colorless oil.

15 TLC R_f 0.24 (silica, 60% EtOAc/hexane)

¹H NMR (400 MHz, d₆-DMSO): δ 7.89 (br t, J=5Hz, 1H), 7.44 (br t, J=6Hz, 1H), 7.40-7.30 (m, 5H), 5.02 (s, 2H), 3.56 (d, J=6Hz, 2H), 3.25 (q, J=6Hz, 2H), 2.35 (t, J=7Hz, 2H), 1.40 (s, 9H).



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19-8

Glycyl-β-alanine t-butyl ester hydrochloride (19-8)

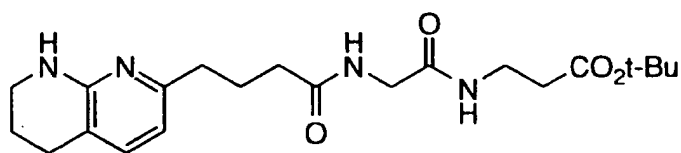
A solution of 19-7 (1.51 g, 4.49 mmol) in 40 mL EtOAc was treated with 10% Pd/C (0.30 g), and a H₂ balloon. After stirring overnight under a hydrogen atmosphere, an additional 200 mg of 10%

25

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Pd/C was added and hydrogenation was continued for 4 h before filtering through Celite and concentrating, providing the free amine as a colorless oil. The amine was dissolved in Et₂O and an excess of 1 M HCl in Et₂O was added. Concentration provided 19-8 as a waxy solid.

- 5 ¹H NMR (free amine, 400 MHz, d₆-DMSO): δ 8.31 (br s, 1H), 5.30 (br s, 2H), 3.29 (q, J=6Hz, 2H), 3.25 (s, 2H), 2.38 (t, J=7Hz, 2H), 1.41 (s, 9H).

19-9

10

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-β-alanine t-butyl ester (19-9)

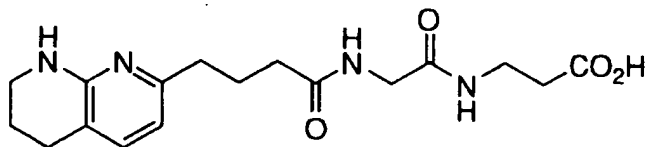
A mixture of 19-5 (62 mg, 0.24 mmol), 19-8 (69 mg, 0.29 mmol), NMM (130 μL, 1.2 mmol) and BOP (160 mg, 0.36 mmol) in 2 mL CH₃CN was stirred overnight. After diluting with EtOAc the mixture was washed with sat. NaHCO₃, water (5x) and brine, dried (MgSO₄), filtered and concentrated, providing 19-9.

TLC R_f 0.79 (silica, 25% NH₃-sat. EtOH/EtOAc)

¹H NMR (300 MHz, CDCl₃): δ 8.50 (br t, 1H), 7.08 (d, J=7Hz, 1H),

- 20 6.64 (br t, 1H), 6.33 (d, J=7Hz, 1H), 5.69 (br s, 1H), 3.99 (d, J=7Hz, 2H), 3.53 (q, J=6Hz, 2H), 3.43 (m, 2H), 2.69 (t, J=6Hz, 2H), 2.60 (t, J=7Hz, 2H), 2.46 (t, J=6Hz, 2H), 2.25 (t, J=7Hz, 2H), 2.05-1.90 (m, 4H), 1.45 (s, 9H).

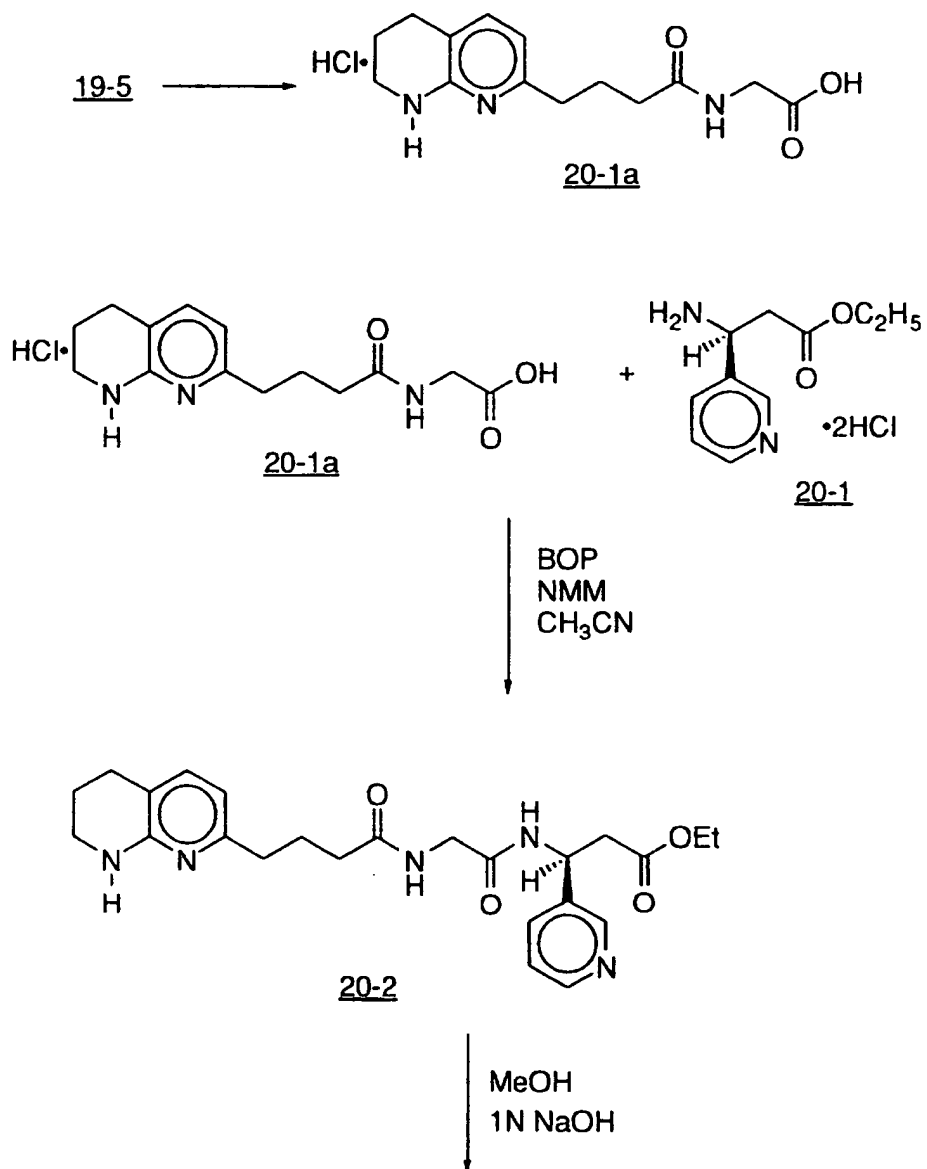
- 148 -

19-10

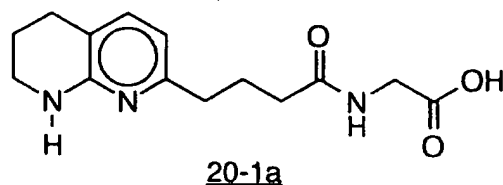
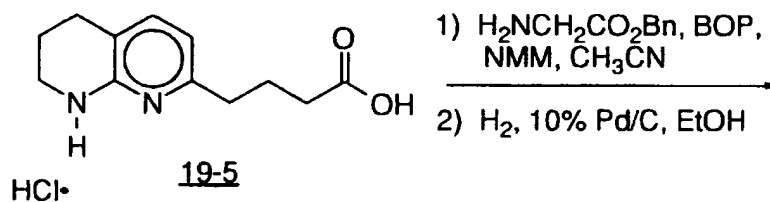
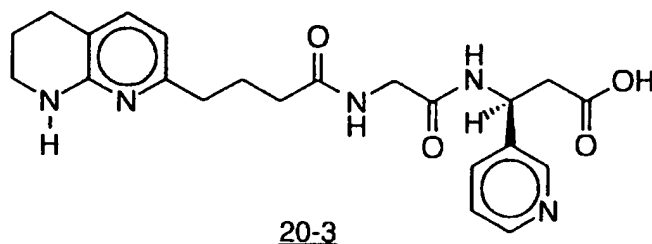
4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl- β -alanine (19-10)

- Ester 19-9 (69 mg, 0.17 mmol) was dissolved in 1 mL
- 5 CH₂Cl₂ at 0°C, 1 mL TFA was added, and the reaction was warmed to ambient temperature for 6 hr. After concentrating and azeotropeing with toluene, flash chromatography (silica, 7:20:1:1 EtOAc/EtOH/H₂O/NH₄OH) provided 19-10 as a white solid. TLC R_f 0.38 (silica, 7:20:1:1 EtOAc/EtOH/H₂O/NH₄OH)
- 10 ¹H NMR (400 MHz, D₂O): δ 7.53 (d, J=7Hz, 1H), 6.59 (d, J=7Hz, 1H), 3.85 (s, 2H), 3.46 (t, J=6Hz, 2H), 3.42 (t, J=7Hz, 2H), 2.78 (t, J=6Hz, 2H), 2.72 (t, J=8Hz, 2H), 2.40 (apparent q, J=7Hz, 4H), 2.00 (qn, J=6Hz, 2H), 1.92 (qn, J=6Hz, 2H).

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SCHEME 20

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5 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl glycine (20-1a)

A mixture of 19-5 (1.02 g, 4.0 mmol), glycine benzyl ester (0.8 g, 4.0 mmol), NMM (1.76 ml, 16 mmol) and BOP (2.03 g, 4.6 mmol) in CH_3CN (100 ml) was stirred overnight. The reaction was concentrated and the residue was partitioned between EtOAc and H_2O .

- 10 The organic layer was washed with sat. NaHCO_3 solution, brine, dried (MgSO_4), filtered and concentrated to a yellow gum which was purified by flash chromatography (silica, 1:1, acetone/ CH_2Cl_2) to provide the ester as a colorless gum.

- 15 A solution of the ester (1.3 g, 3.5 mmol) in EtOH (100 ml) was hydrogenated at 1 atm for 18 hr. The reaction was diluted with EtOAc (200 ml) to dissolve the product, filtered and concentrated to a solid which was sonicated with ether (100 ml) to provide 20-1a as a colorless solid.

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TLC R_f 0.35 (silica, EtOH/NH₃)

¹H NMR (300 MHz, CD₃OD): δ 7.50 (d, J=7Hz, 2H), 6.59 (d, J=7Hz, 2H), 3.80 (s, 2H), 3.47 (t, J=6Hz, 2H), 2.79 (t, J=6Hz, 2H), 2.72 (t, J=7Hz, 2H), 2.26 (t, J=7Hz, 2H), 2.02 (m, 2H), 1.94 (m, 2H).

5

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)-pyridin-3-yl-β-alanine ethyl ester (20-2)

The CH₃CN solution (300 mL) of 20-1a (164 mg, 0.59 mmol), 20-1 (Rico *et al.*, *J. Org. Chem.*, 1993, 58, 7948) (158 mg, 0.58 mmol), NMM (260 μl, 2.36 mmol) and BOP (300 mg, 0.68 mmol) was stirred under ambient conditions for 48 h. The reaction was concentrated to a yellow gum which was purified by flash chromatography (silica, 9:1 CH₂Cl₂/EtOH•NH₃) to provide 20-2 as a colorless gum.

15 R_f 0.21 (silica, 9:1 CH₂Cl₂/EtOH•NH₃)

¹H NMR (300 MHz, CD₃OD): δ 8.53 (bs, 1H), 8.42 (d, J=5Hz, 1H), 7.82 (d, J=8Hz, 1H), 7.39 (dd, J=8Hz, 5Hz, 1H), 7.10 (d, J=8Hz, 1H), 6.36 (d, J=7Hz, 1H), 5.40 (t, J=7Hz, 1H), 4.07 (q, J=7Hz, 2H), 3.85 (s, 2H), 3.36 (t, J=6Hz, 2H), 2.91 (m, 2H), 2.68 (t, J=6Hz, 2H), 2.51 (t, J=7Hz, 2H), 2.23 (t, J=7Hz, 2H), 1.89 (m, 4H), 1.16 (t, J=7Hz, 3H).

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4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)-pyridin-3-yl-β-alanine (20-3)

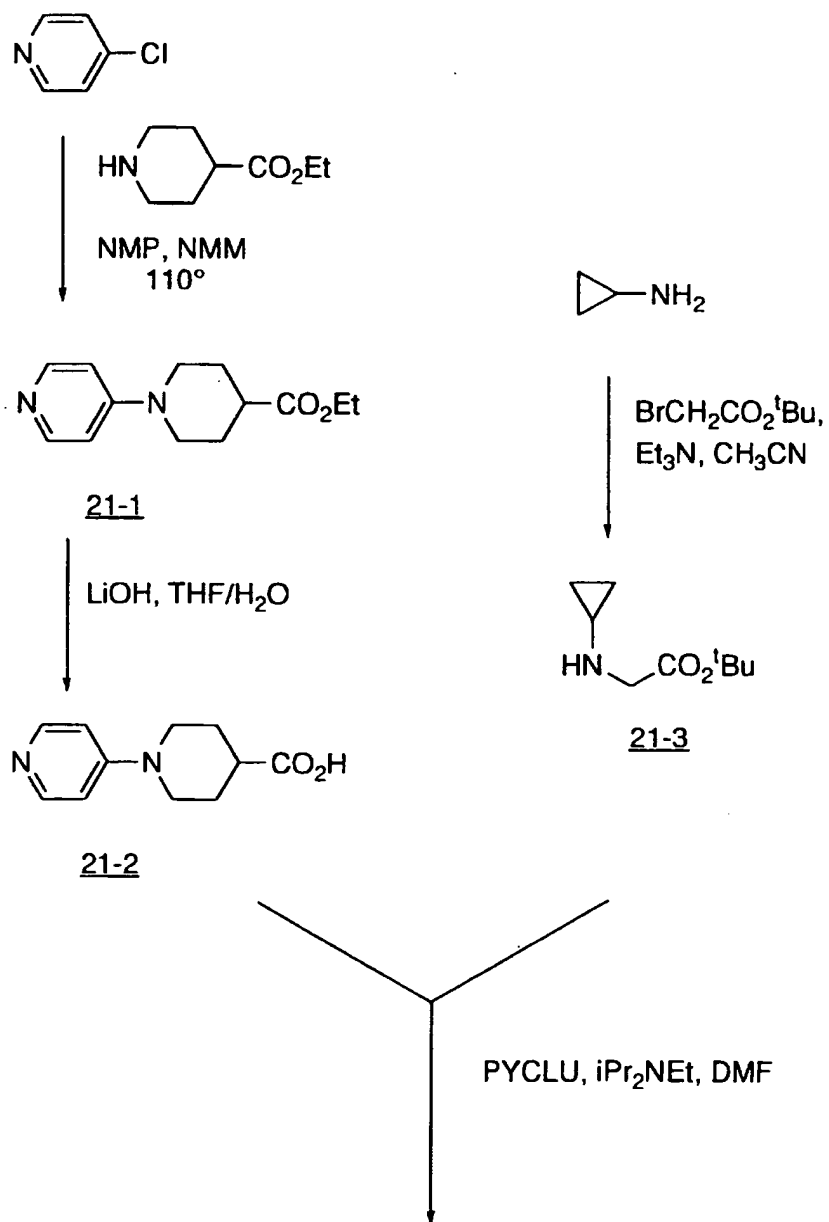
A methanol solution (10 mL) of 20-2 (190 mg, 0.42 mmol) and 1N NaOH (2.1 mL, 2.1 mmol) was stirred under ambient conditions for 18 h. The reaction was concentrated to dryness and the residue neutralized with 1N HCl and the resultant solution concentrated to a gum which was chromatographed (silica, 38/1/1 EtOH/NH₄OH/H₂O) to provide a solid which was purified by HPLC using a VyOAC C₁₈ semi prep column with gradient elution [95:5(99.9:0.1 H₂O/TFA)/(99.9:0.1 CH₃CN/TFA) → 50:50 (99.9:0.1 H₂O/TFA)/(99.9:0.1 CH₃CN/TFA) 80 min] to provide 20-3 as a hygroscopic solid ditrifluoroacetate salt. R_f 0.36 (silica 38:1:1 EtOH/NH₄OH/H₂O)

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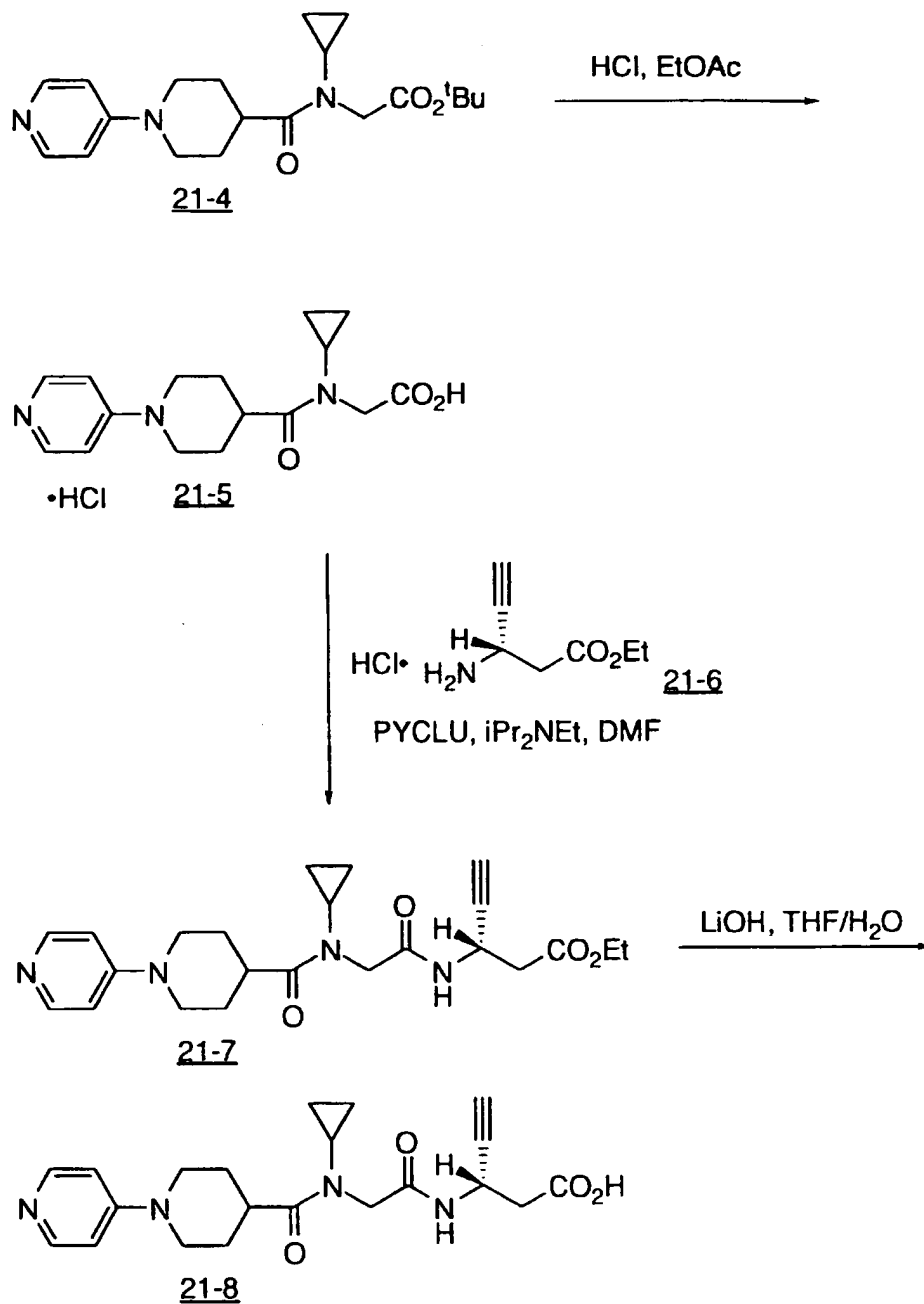
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^1H NMR (300 MHz, CD_3OD): δ 8.79 (bs, 1H), 8.65 (d, $J=5\text{Hz}$, 1H), 8.7 (d, $J=8\text{Hz}$, 1H), 7.84 (m, 1H), 7.57 (d, $J=7\text{Hz}$, 1H), 6.61 (d, $J=7\text{Hz}$, 1H), 5.44 (t, $J=7\text{Hz}$, 4H), 3.88 (m, 2H), 3.48 (t, $J=5\text{Hz}$, 2H), 2.98 (d, $J=7\text{Hz}$, 2H), 2.81 (t, $J=6\text{Hz}$, 2H), 2.70 (m, 2H), 2.31 (m, 2H), 1.96 (m, 4H).

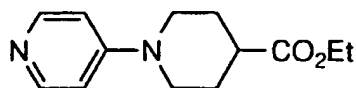
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SCHEME 21

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SCHEME 21 (CONT'D)

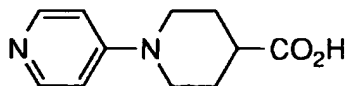
- 155 -

21-1Ethyl N-pyridin-4-ylisonipecotate (21-1)

5 Ethyl isonipecotate (6.0 g, 38.66 mmol), 4-chloropyridine hydrochloride (5.9 g, 38.66 mmol) and N-methylmorpholine (9.3 mL, 85.0 mmol) were dissolved in N-methylpyrrolidinone (50 mL) and the resulting solution heated at 100° for 48 h. The solution was concentrated *in vacuo* and the residue dissolved in ethyl acetate (200 mL), washed with water and brine (2 x 100 mL), then dried (Na₂SO₄) and evaporated. The resulting residue was purified by flash
10 chromatography (5% MeOH/CH₂Cl₂) to afford 21-1 as a crystalline solid.

¹H NMR (300 MHz, CDCl₃) δ 8.21 (d, J=6.8Hz, 2H), 6.78 (d, J=6.8Hz, 2H), 4.18 (q, J=7.0Hz, 2H), 3.85 (m, 2H), 3.10 (m, 2H), 2.61 (m, 1H) 2.05 (m, 2H), 1.85 (m, 2H), 1.23 (t, J=7.0Hz, 3H).

15

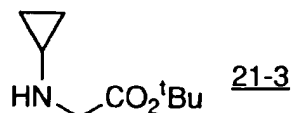
21-2N-Pyridin-4-ylisonipecotic acid (21-2)

A solution of ester 21-1 (10 g, 42.7 mmol) in THF (50 mL) was treated with 1N LiOH (47 mL, 47.0 mmol) and H₂O (50 mL). The
20 resulting solution was concentrated and the aqueous residue cooled to 0°C, then adjusted to pH 6 with 1N HCl and the resulting solid 21-2, collected by filtration.

¹H NMR (300 MHz, D₂O) δ 7.95 (d, 6.8Hz, 2H), 6.73 (d, 6.8Hz, 2H), 3.76 (d, J=12.8Hz, 2H), 2.81 (m, 2H), 2.20 (m, 1H), 1.85 (d, J=12.8Hz, 2H), 1.55 (m, 2H).

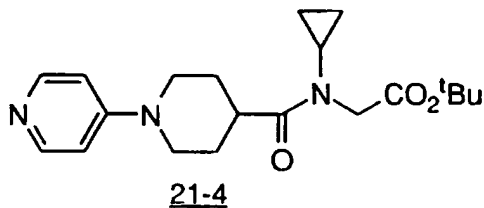
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tert-Butyl-N-cyclopropylglycine (21-3)

A mixture of cyclopropylamine (10.0 g, 175.1 mmol) and triethylamine (4.9 ml, 35.5 mmol) in 100 ml CH₂Cl₂ was cooled to 0° and treated with tert-butyl bromoacetate (5.25 ml, 35.0 mmol). The resulting mixture was stirred at 0°C for 2 h, refluxed for 1.5 h, then cooled and washed with sat. NaHCO₃, and brine (50 ml each) then dried (Na₂SO₄) and evaporated to afford 21-3 a colorless oil.

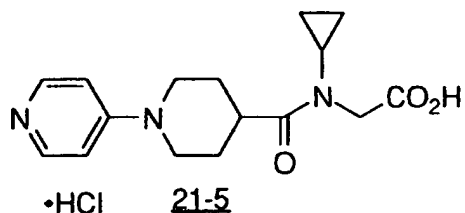
¹H NMR (300 MHz, CDCl₃) δ 3.35 (s, 2H), 2.19 (m, 1H), 2.08 (br s, 1H), 1.48 (s, 9H), 0.47 (m, 2H), 0.38 (m, 2H).

tert-Butyl N-pyridin-4-ylisonipecotyl-N-cyclopropylglycine (21-4)

A solution of acid 21-2 (500 mg, 2.36 mmol), ester 21-4 (404 mg, 2.36 mmol), chloro-N,N,N',N'-bis(pentamethylene)-formamidinium hexafluorophosphate (PYCLU) (851 mg, 2.36 mmol), and diisopropylethyl amine (305 mg, 2.36 mmol) in anhydrous DMF (50 mL) was stirred at room temperature for 18 h then concentrated *in vacuo* to afford a yellow residue. Chromatography on silica gel (1:1 MeOH/EtOAc) afforded 21-4 as a crystalline solid.

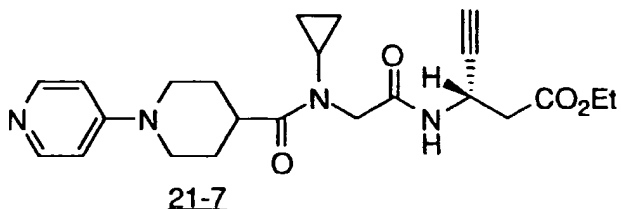
¹H NMR (300 MHz, CD₃OD) δ 8.12 (d, J=6.8 Hz, 2H), 6.75 (d, J=6.8Hz, 2H), 3.94 (d, J=12.8Hz, 2H), 3.85 (s, 2H), 2.81 (m, 2H), 1.95 (m, 2H), 1.85 (m, 2H), 1.55 (m, 2H), 1.42 (s, 9H), 0.47 (m, 2H), 0.38 (m, 2H).

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N-Pyridin-4-ylisonipecotyl-N-cyclopropylglycyl (21-5)

Ester **21-5** (250 mg, 0.70 mmol) was suspended in EtOAc (25 mL), cooled to 0° and treated with HCl gas for 15 min. The resulting solution was stirred at 0° for 3.5 h then evaporated to give **21-5** as a yellow glass.

¹H NMR (300 MHz, CD₃OD) δ 8.18 (d, J=6.8Hz, 2H), 7.18 (d, J=6.8Hz, 2H), 4.24 (d, J=12.8Hz, 2H), 3.95 (s, 2H), 3.21 (m, 2H), 1.95 (m, 2H), 1.85 (m, 2H), 1.62 (m, 2H), 0.87 (m, 2H), 0.75 (m, 2H).

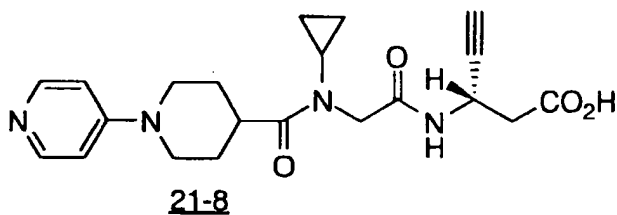
Ethyl N-pyridin-4-ylisonipecotyl-N-cyclopropylglycyl-3(S)-ethynyl-β-alanine (21-7)

A solution of acid **21-5** (232 mg, 0.68 mmol), ester **21-6** (121 mg, 0.68 mmol) (**21-6** prepared as described in U.S. patent 5,272,162), PYCLU (245 mg, 0.68 mmol), and diisopropylethyl amine (176 mg, 0.68 mmol) in anhydrous DMF (50 ml) was stirred at room temperature for 18 h then concentrated *in vacuo* to afford a yellow residue. Preparative reverse phase chromatographic purification afforded ester **21-7** as its TFA salt.

¹H NMR (300 MHz, CD₃OD) δ 8.48 (d, J=6.8Hz, 1H), 8.08 (d, J=6.8Hz, 2H), 7.18 (d, J=6.8Hz, 2H), 5.01 (m, H), 4.24 (d, J=12.8Hz, 2H), 4.12 (q, J=7Hz, 2H), 3.99 (s, 2H), 3.72 (m, 1H), 3.31 (m, 2H), 2.95

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(m, 1H), 2.73 (m, 2H), 1.95 (m, 2H), 1.85 (m, 2H), 1.21 (t, J=7.0Hz, 2H), 0.87 (m, 2H), 0.75 (m, 2H).

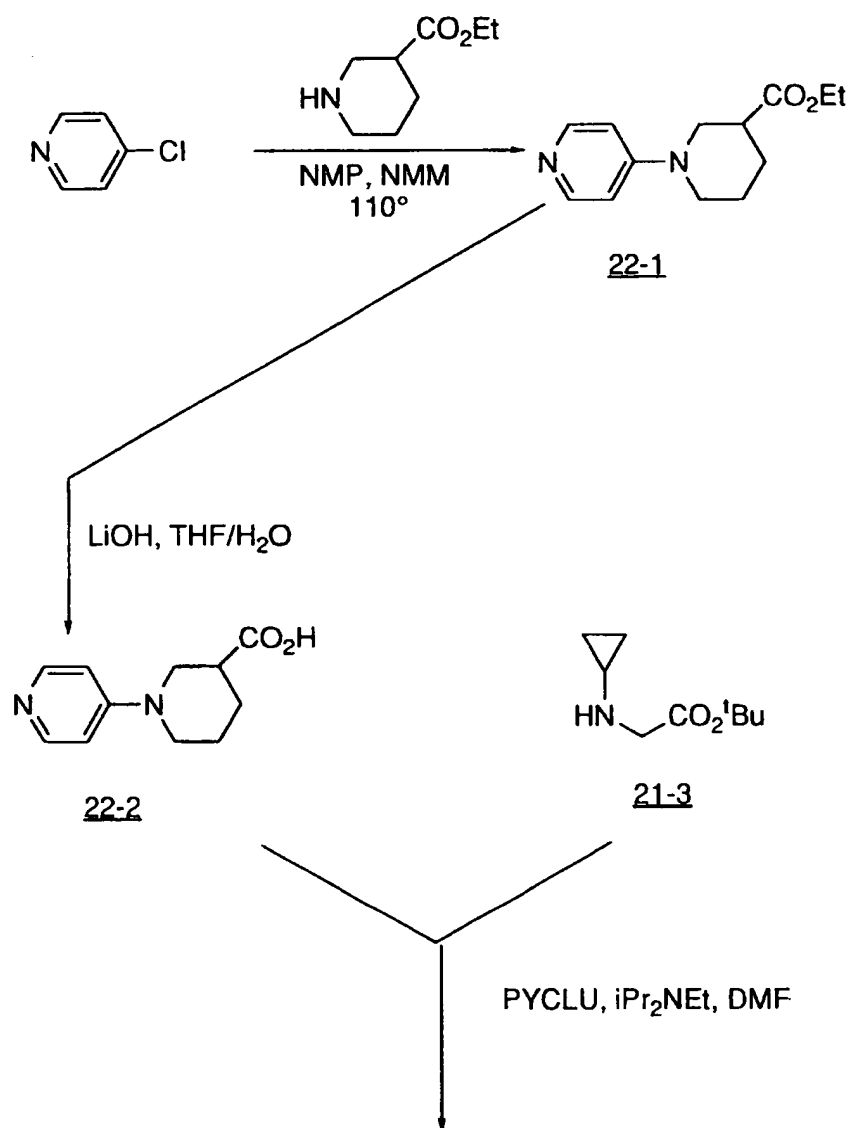


5 N-Pyridin-4-ylisonipecotyl-N-cyclopropylglycyl -3(S)-ethynyl- β -alanine (21-8)

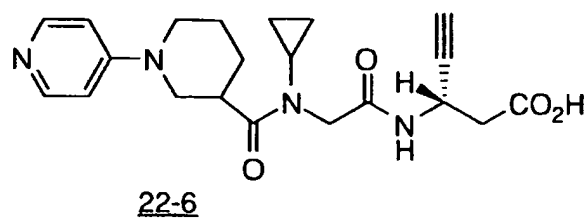
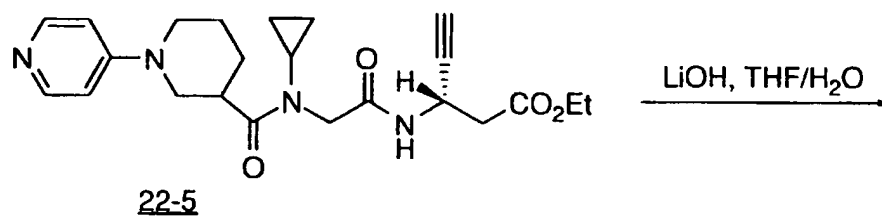
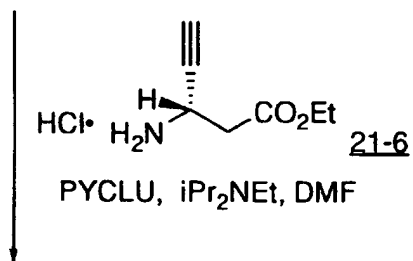
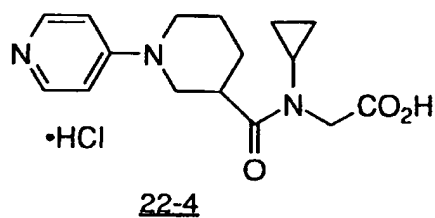
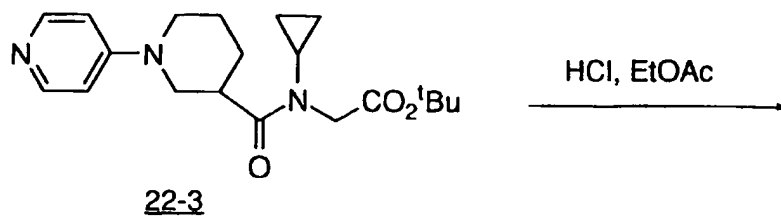
A solution of ester 21-7 (180 mg, 0.422 mmol), in THF (10 mL) was treated with 1N LiOH (0.84 mL, 0.84 mmol) and stirred at room temperature for 16 h. The mixture was concentrated and the residue purified by preparative reverse phase chromatography to afford 19-8 as its TFA salt.

¹H NMR (300 MHz, CD₃OD) δ 8.40 (d, J=6.8Hz, 1H), 8.21 (d, J=6.8Hz, 2H), 7.21 (d, J=6.8Hz, 2H), 4.81 (m, 1H), 4.22 (d, J=12.8Hz, 2H), 3.99 (m, 2H), 3.72 (m, 1H), 3.31 (m, 2H), 2.95 (m, 1H), 2.76 (m, 1H), 2.71 (m, 2H), 1.95 (m, 2H), 1.85 (m, 2H), 0.87 (m, 2H), 0.75 (m, 2H).

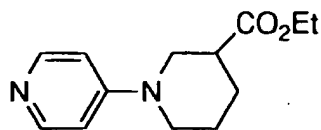
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SCHEME 22

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SCHEME 22 (CONT'D)

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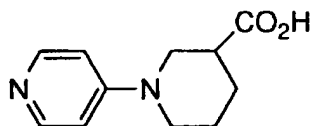
22-1Ethyl N-pyridin-4-yl nipecotate (22-1)

Ethyl (+) nipecotate (7.0 g, 44.53 mmol) was reacted with 4-chloropyridine hydrochloride (6.67 g, 44.53 mmol) as described for

5 21-1 to give the title compound as a yellow solid.

¹H NMR (300 MHz, CDCl₃) δ 8.22 (d, J=6.8Hz, 2H), 6.68 (d, J=6.8Hz, 2H), 4.18 (q, J=7.0Hz, 2H), 3.85 (m, 1H), 3.72 (m, 1H), 3.21 (m, 1H), 3.10 (m, 1H), 2.60 (m, 1H), 2.08 (m, 1H), 1.81 (m, 2H), 1.60 (m, 1H), 1.13 (t, J=7.0Hz, 3H).

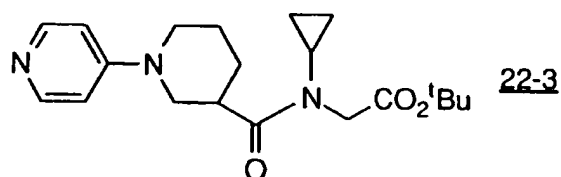
10

22-2N-Pyridin-4-yl nipecotic acid (22-2)

Prepared from 22-1 (764 mg, 3.25 mmol) in a manner similar to that described for 21-2.

15 ¹H NMR (300 MHz, DMSO-d₆) δ 8.13 (d, J=6.8Hz, 2H), 6.74 (d, J=6.8Hz, 2H), 4.08 (d, 1H), 3.78 (m, 1H), 2.92 (m, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.71 (m, 1H), 1.42 (m, 2H).

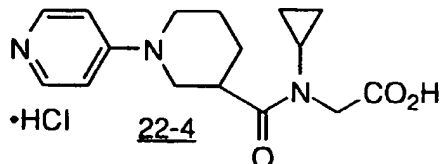
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tert-Butyl N-pyridin-4-ylnipecotyl-N-cyclopropylglycine (22-3)

5 Prepared from 22-2 (320 mg, 1.51 mmol) and 21-3 (258 mg, 1.51 mmol) in a manner similar to that described for 21-4.

¹H NMR (300 MHz, CDCl₃) δ 8.12 (d, 6.8Hz, 2H), 6.62 (d, J=6.8Hz, 2H), 3.94 (s, 2H), 3.85 (m, 1H), 3.12 (m, 1H), 3.08 (m, 1H), 2.51 (m, 2H), 1.95 (m, 1H), 1.85 (m, 2H), 1.58 (m, 2H), 1.42 (s, 9H), 0.47 (m, 10 2H), 0.38 (m, 2H).

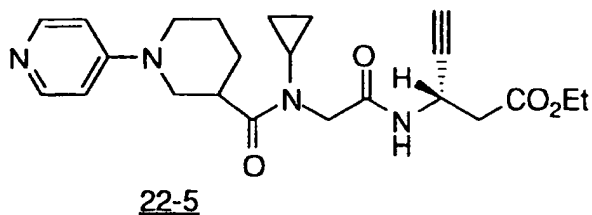


N-Pyridin-4-ylnipecotyl-N-cyclopropylglycine hydrochloride (22-4)

15 Ester 22-3 (250 mg, 0.70 mmol) was suspended in EtOAc (25 mL), cooled to 0° and treated with HCl gas for 15 min. The resulting solution was stirred for 3.5 h then evaporated to give 22-4 as a white solid.

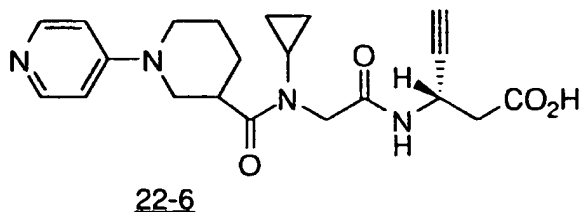
¹H NMR (300 MHz, DMSO-d₆) δ 8.18 (d, J=6.8Hz, 2H), 7.18 (d, J=6.8Hz, 2H), 4.24 (d, J=12.8Hz, 2H), 3.95 (m, 2H), 3.21 (m, 1H), 1.94 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.53 (m, 1H), 0.87 (m, 2H), 0.75 (m, 2H). 20

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Ethyl N-pyridin-4-ylnipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine (22-5)

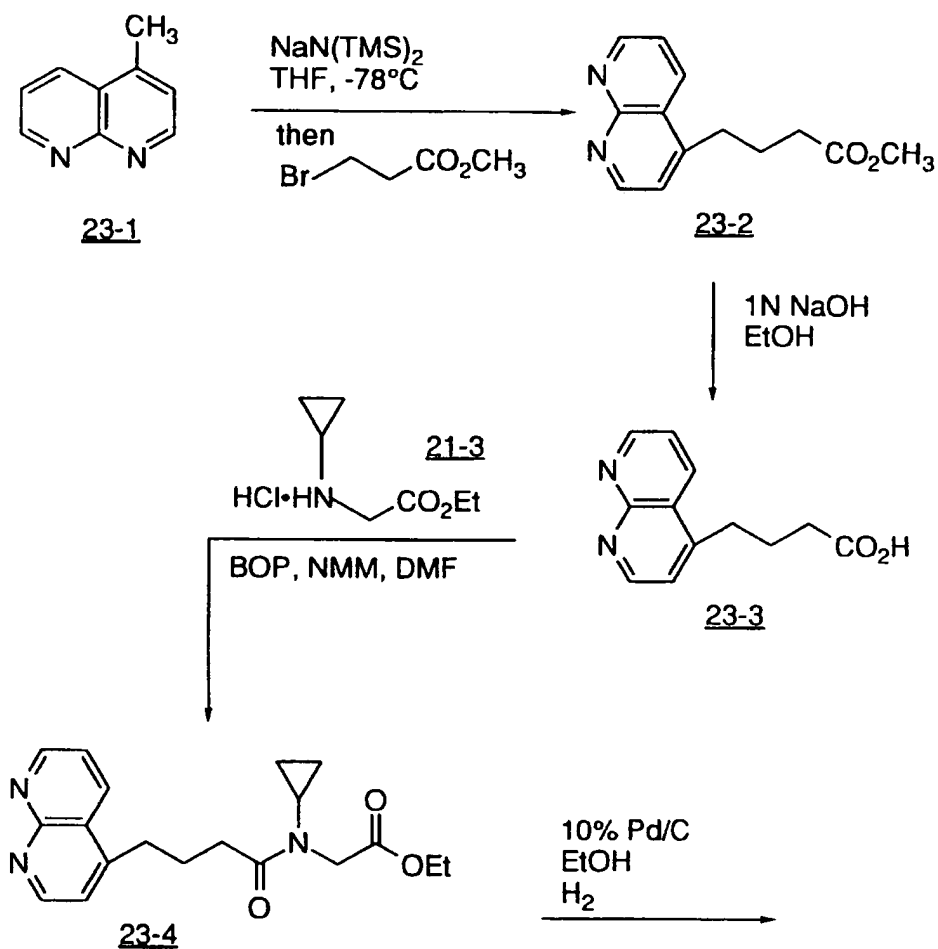
- Prepared from 22-4 (195 mg, 0.60 mmol) in a manner similar to that described for 21-7.
 ^1H NMR (300 MHz, CD_3OD) δ 8.49 (d, $J=6.8\text{Hz}$, 1H), 8.17 (d, $J=6.8\text{Hz}$, 2H), 7.21 (d, $J=6.8\text{Hz}$, 2H), 5.15 (m, 1H), 4.26 (m, 1H), 4.21 (d, 1H), 4.08 (q, 2H), 3.82 (m, 1H), 3.5-3.3 (m, 3H), 2.95 (m, 1H), 2.76 (m, 1H), 2.71 (m, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.81 (m, 1H), 1.72 (m, 1H), 1.21 (t, 3H), 0.87 (m, 2H).



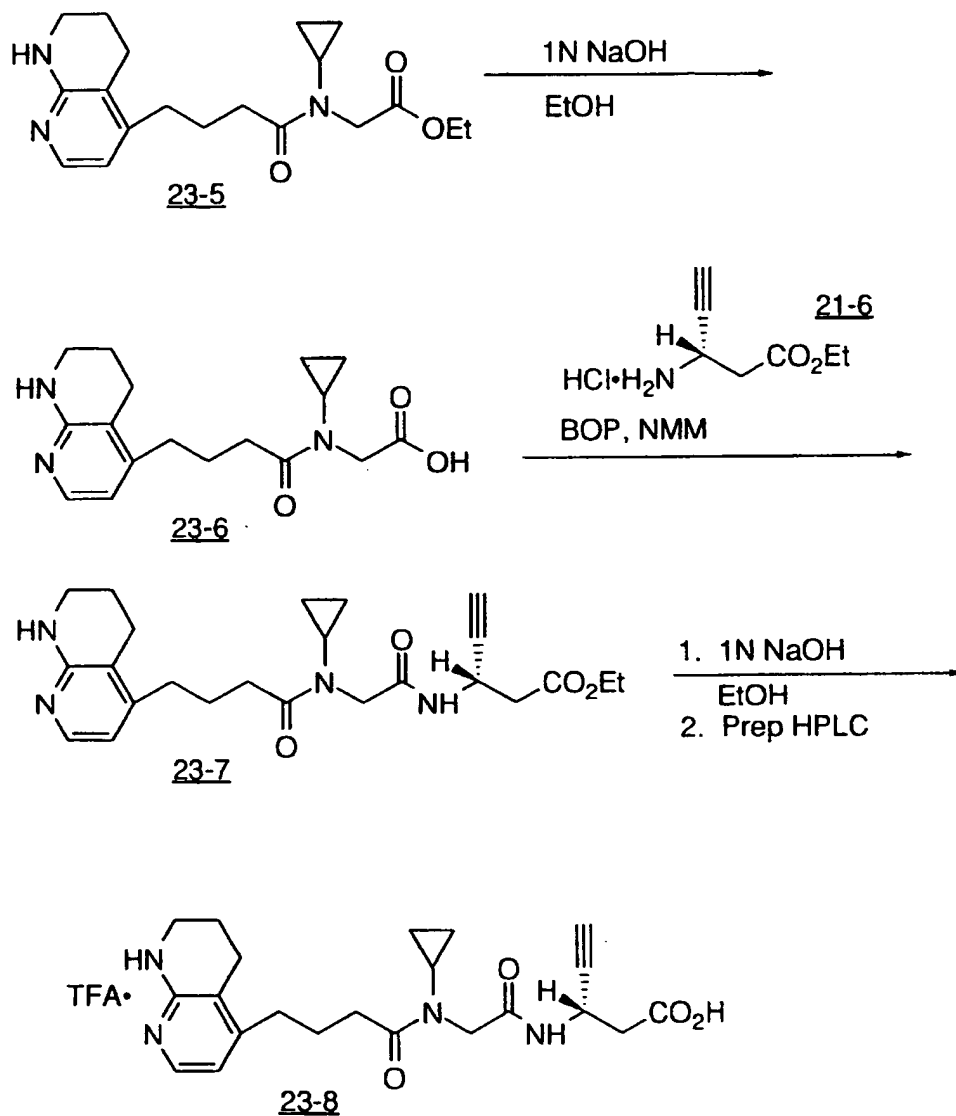
N-Pyridin-4-ylnipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine (22-6)

- Prepared from 22-4 (20 mg, 0.04 mmol) in a manner similar to that described for 21-8.
 FAB mass spectrum $m/z = 399$ ($M + 1$).
 ^1H NMR (300 MHz, CD_3OD) δ 8.16 (d, $J=6\text{Hz}$, 2H), 6.91 (d, $J=6.8\text{Hz}$, 2H), 5.05 (m, 1H), 4.26 (d, $J=6\text{Hz}$, 1H), 4.21 (d, 1H), 3.82 (m, 1H), 3.5-3.3 (m, 3H), 2.95 (m, 1H), 2.76 (m, 1H), 2.71 (m, 2H), 2.15 (m, 1H), 1.95 (m, 1H), 1.81 (m, 1H), 1.72 (m, 1H), 1.21 (t, 1H), 0.87 (m, 2H).

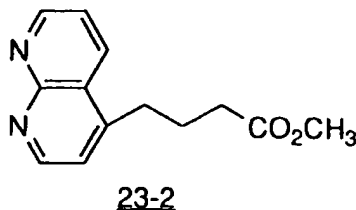
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SCHEME 23

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SCHEME 23 (CONT'D)

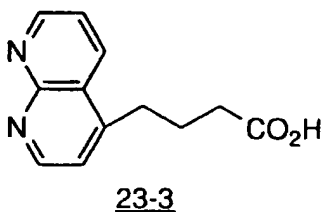
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Methyl 4-(1,8-naphthyridin-4-yl)butyrate (23-2)

To a stirred solution of naphthyridine 23-1 (Hamada, Y. *et al.*, *Chem. Pharm. Bull. Soc.*, 1971, 19(9), 1857-1862), (2.2 g, 15.2 mmol) and THF (200 ml) at -78°C was added NaN(TMS)₂ (1M/THF, 18 ml, 18 mmol) dropwise over a 20 min period. After 30 minutes at -78°C, methyl 3-bromopropionate was added in a stream. After 30 min, the reaction was quenched with 50 ml 10% KHSO₄. The mixture was extracted with Et₂O. The remaining aqueous portion was basified with sat. NaHCO₃ and then extracted with EtOAc. The EtOAc portion was washed with brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 2% EtOH/EtOAc) gave the ester 23-2 (1.61 g) as a yellow oil.

TLC R_f = 0.27 (silica, 2% EtOH/EtOAc)
¹H NMR (400 MHz, CDCl₃) δ 9.14 (m, 1H), 9.35 (d, J=4Hz, 1H), 8.50 (d, J=7Hz, 1H), 7.52 (q, J=4Hz, 1H), 7.33 (d, J=4Hz, 1H), 3.71 (s, 3H), 3.14 (t, J=8Hz, 2H), 2.46 (t, J=7Hz, 2H), 2.09 (m, 2H).



4-(1,8-Naphthyridin-4-yl)butanoic acid (1-3)

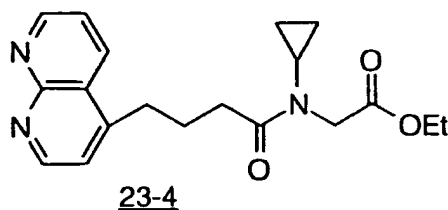
A solution of ester 23-2 (1.60 g, 6.9 mmol), 1N NaOH (7 ml, 7 mmol) and EtOH (20 ml) was stirred at ambient temperature for 1.0 h. The solution was extracted with Et₂O. The aqueous portion was neutralized with concentrated HCl (583 μl, 7.0 mmol). The precipitate

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was collected, washed with Et₂O, and dried *in vacuo* to furnish carboxylic acid 23-3 as a tan solid.

TLC R_f = 0.59 (silica, 20:1:1 CH₂Cl₂/MeOH/AcOH)

¹H NMR (400 MHz, CD₃OD) δ 9.05 (q, J=2H, 1H), 8.95 (d, J=4H, 1H),
5 8.77 (dd, J=2Hz, 8Hz, 1H), 7.67 (q, J=4H, 1H), 7.53 (d, J=4Hz, 1H),
3.22 (t, J=8Hz, 2H), 2.46 (t, J=7Hz, 2H), 2.03 (m, 2H).



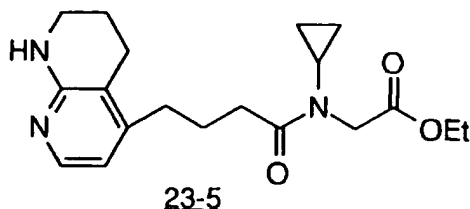
10 4-(1,8-Naphthyridin-4-yl)butanoyl-N-(cyclopropyl)glycine ethyl ester
(23-4)

A solution of acid 23-3 (400 mg, 1.84 mmol), amine 21-3 (331 mg, 1.84 mmol), BOP reagent (979 mg, 2.21 mmol), NMM (1.03 ml, 7.36 mmol) and DMF (20 ml) was stirred at ambient temperature for 20 h. The solution was diluted with ethyl acetate and then washed
15 with sat. NaHCO₃, brine, dried (MgSO₄) and concentrated. Flash chromatography (silica, 10:1 EtOAc/sat. NH₃-EtOH) furnished ester 23-4 (600 mg) as an orange solid.

TLC R_f = 0.15 (silica, 10:1 EtOAc/sat. NH₃-EtOH)

¹H NMR (300 MHz, CDCl₃) δ 9.12 (m, 1H), 9.03 (d, J=4Hz, 1H), 8.62
20 (dd, J=2Hz, 8Hz, 1H), 7.53 (q, J=4Hz, 1H), 7.38 (d, J=4Hz, 1H), 4.20
(q, J=7Hz, 2H), 4.13 (s, 2H), 3.19 (t, J=8Hz, 2H), 2.79 (m, 1H), 2.70
(m, 2H), 2.13 (m, 2H), 1.29 (t, J=8Hz, 3H), 0.85 (m, 2H), 0.74 (m, 2H).

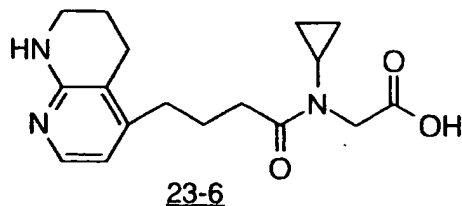
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4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycine ethyl ester (23-5)

- A mixture of ester 23-4 (600 mg, 1.75 mmol), 10% Pd/C (300 mg) and EtOH (30 ml) was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 20 h. The catalyst was removed by filtration through celite and then the filtrate was concentrated. Flash chromatography (silica, 50%/EtOAc/sat. NH₃-EtOH) gave ester 23-5 as a colorless oil.
- 10 TLC R_f = 0.25 (silica, 50:1 EtOAc/sat. NH₃-EtOH)
¹H NMR (400 MHz, CD₃OD) δ 7.58 (d, J=6Hz, 1H), 6.48 (d, J=6Hz, 1H), 4.15 (q, J=7Hz, 2H), 4.08 (s, 2H), 3.36 (t, J=5Hz, 2H), 2.86 (m, 1H), 2.75 (t, J=6Hz, 2H), 2.68 (t, J=7Hz, 2H), 2.60 (t, J=8Hz, 2H), 1.90 (m, 4H), 1.25 (t, J=7Hz, 3H), 0.87 (m, 2H), 0.78 (m, 2H).

15



4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycine (23-6)

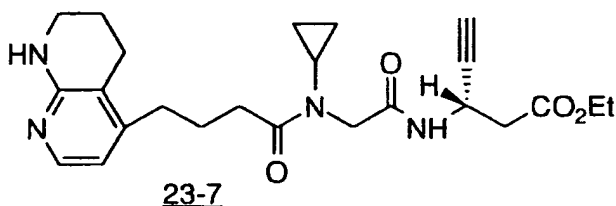
- A solution of ester 23-5 (200 mg, 0.5774 mmole), 1N NaOH (600 μl, 0.600 mmole) and CH₃OH was stirred at ambient temperature for 1.5 h. The solution was concentrated. The residue was dissolved in 1N HCl (600 μl) and then the solution was concentrated. The residue was dissolved in CHCl₃, filtered and concentrated to give the carboxylic acid 23-6 (110 mg) as a white solid.
- 20

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TLC R_f = 0.14 (silica, 10:1:1 CH₂Cl₂/MeOH/AcOH)

¹H NMR (300 MHz, CD₃OD) δ 7.56 (d, J=6Hz, 1H), 6.64 (d, J=6Hz, 1H), 3.98 (s, 2H), 3.41 (t, J=6Hz, 2H), 2.89 (m, 1H), 2.81 (t, J=6Hz, 2H), 2.71 (m, 4H), 1.88 (m, 4H), 0.82 (m, 4H).

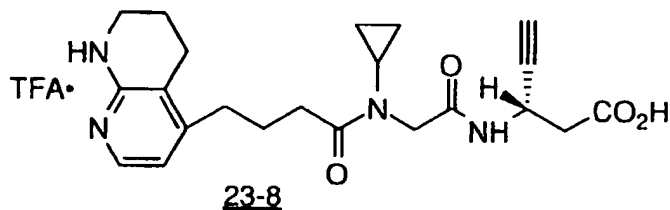
5



4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)-ethynyl-β-alanine ethyl ester (23-7)

- To a stirred solution of acid 23-6 (40 mg, 0.1256 mmol),
 10 amine 21-6 (33 mg, 0.1884 mmol), NMM (70 μl, 0.5024 mmol) and
 CH₃CN (1 ml) was added BOP reagent (61 mg, 0.1382 mmol). After
 20 h at ambient temperature, the solution was diluted with ethyl acetate
 and then washed with sat. NaHCO₃, brine, dried (MgSO₄) and
 concentrated. Flash chromatography (silica, 40:1:1
 15 CH₂Cl₂/MeOH/AcOH) gave the ester 23-7 as a colorless oil.
 TLC R_f = 0.23 (silica, 40:1:1 CH₂Cl₂/MeOH/AcOH)
¹H NMR (300 MHz, CD₃OD) δ 7.58 (d, J=6Hz, 1H), 6.66 (d, J=6Hz,
 1H), 5.01 (m, 1H), 4.13 (q, J=7Hz, 2H), 4.02 (s, 2H), 3.42 (t, J=6Hz,
 2H), 2.72 (m, 10H), 1.95 (m, 4H), 1.24 (t, J=7Hz, 3H), 0.85 (m, 2H),
 20 0.78 (m, 2H).

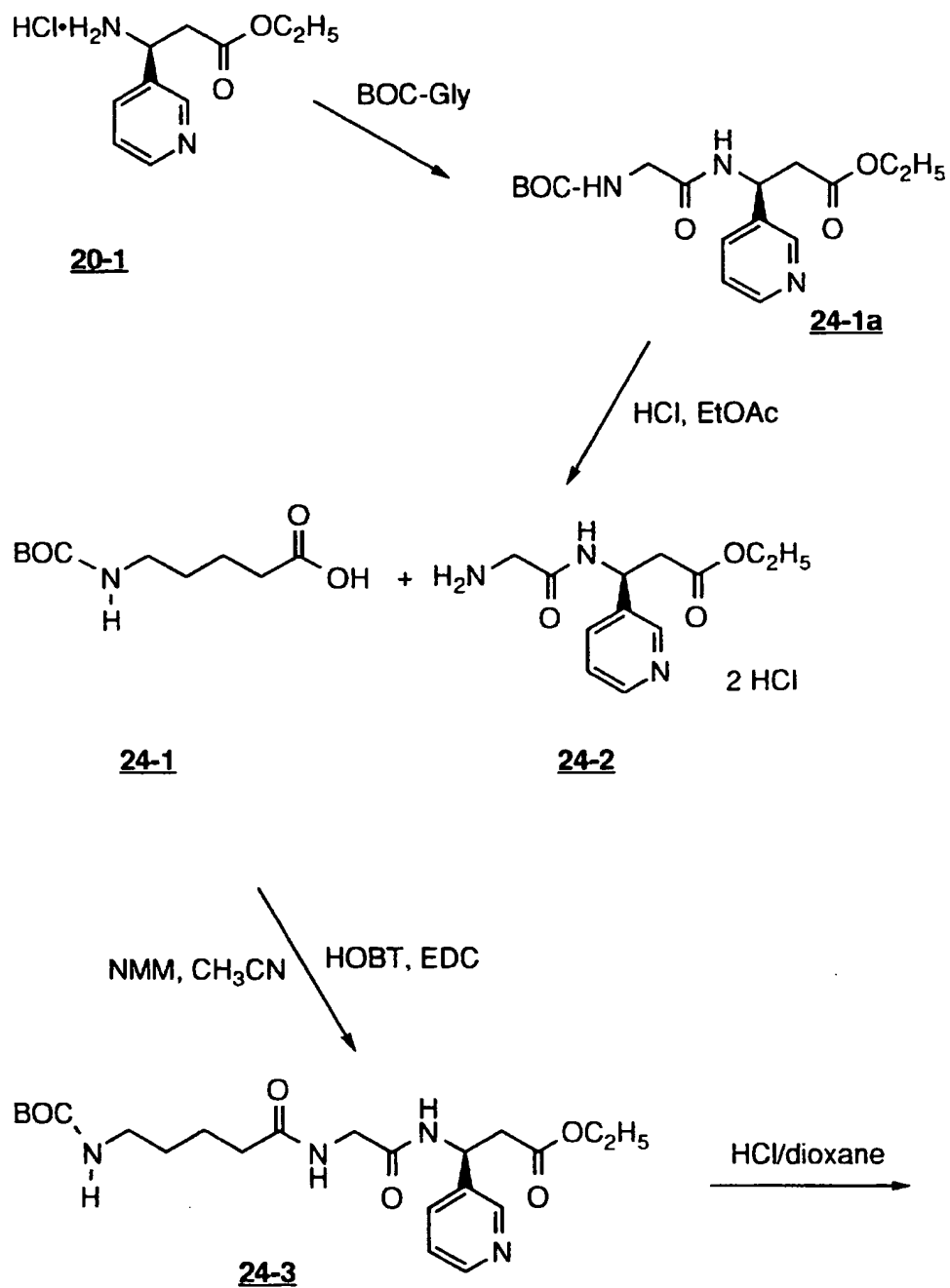
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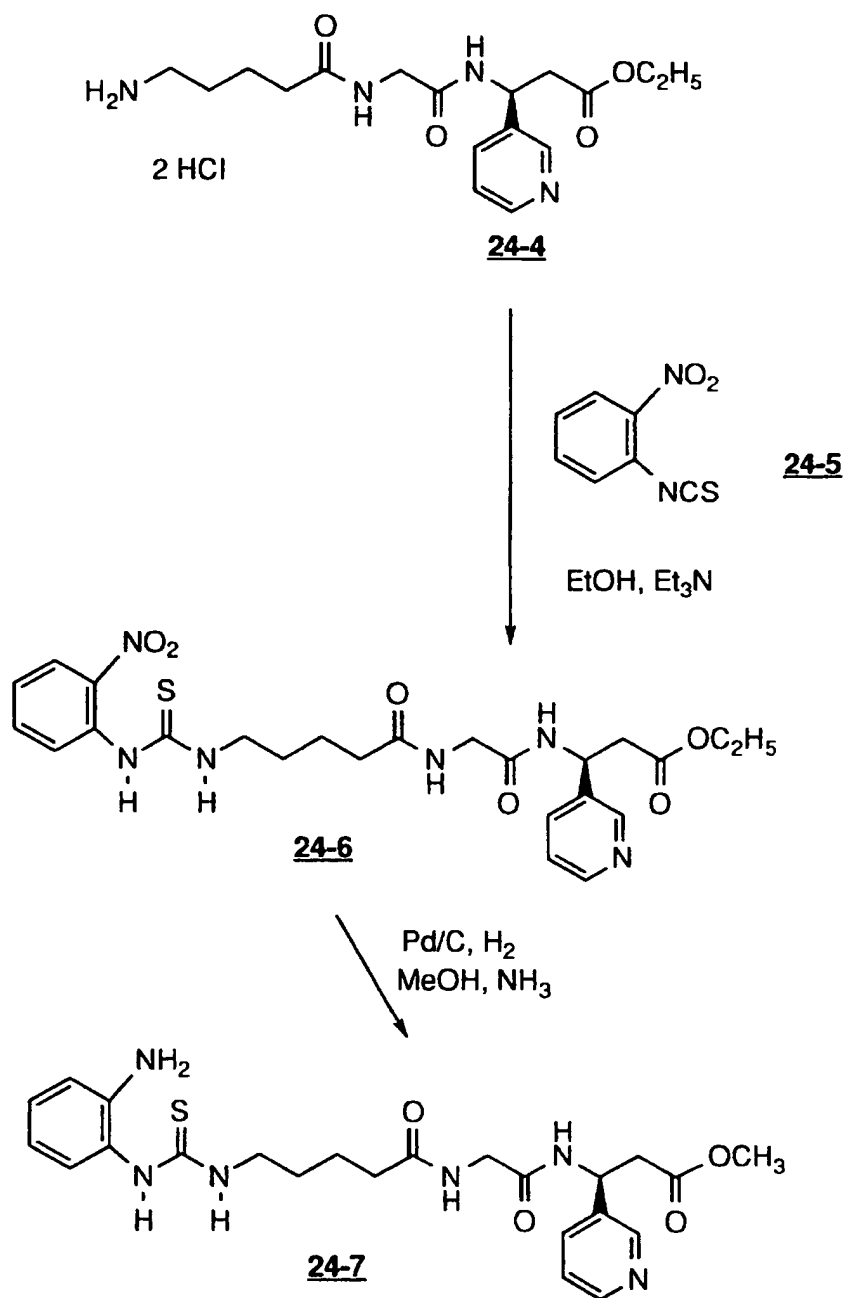
4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)-ethynyl- β -alanine (23-8)

- A solution of ester 23-7 (32 mg, 0.0725 mmol), 1N NaOH (100 μ l) and CH₃OH (500 ml) was stirred at ambient temperature for 1.0 h. The solution was concentrated. The residue was dissolved in 1N HCl (100 μ l) and then concentrated. Preparative HPLC purification (C₁₈, H₂O/CH₃CN/TFA) provided acid 23-8 as a TFA salt. TLC R_f = 0.50 (silica, 10:1:1 EtOH/NH₄OH/H₂O)
- ¹H NMR (300 MHz, CD₃OD) δ 8.43 (d, J=9Hz, 1H), 7.58 (d, J=7Hz, 1H), 6.76 (d, J=7Hz, 1H), 4.99 (m, 1H), 4.03 (d, J=3Hz, 2H), 3.46 (t, J=5Hz, 2H), 2.72 (m, 10H), 1.95 (m, 4H), 0.87 (m, 2H), 0.79 (m, 2H).

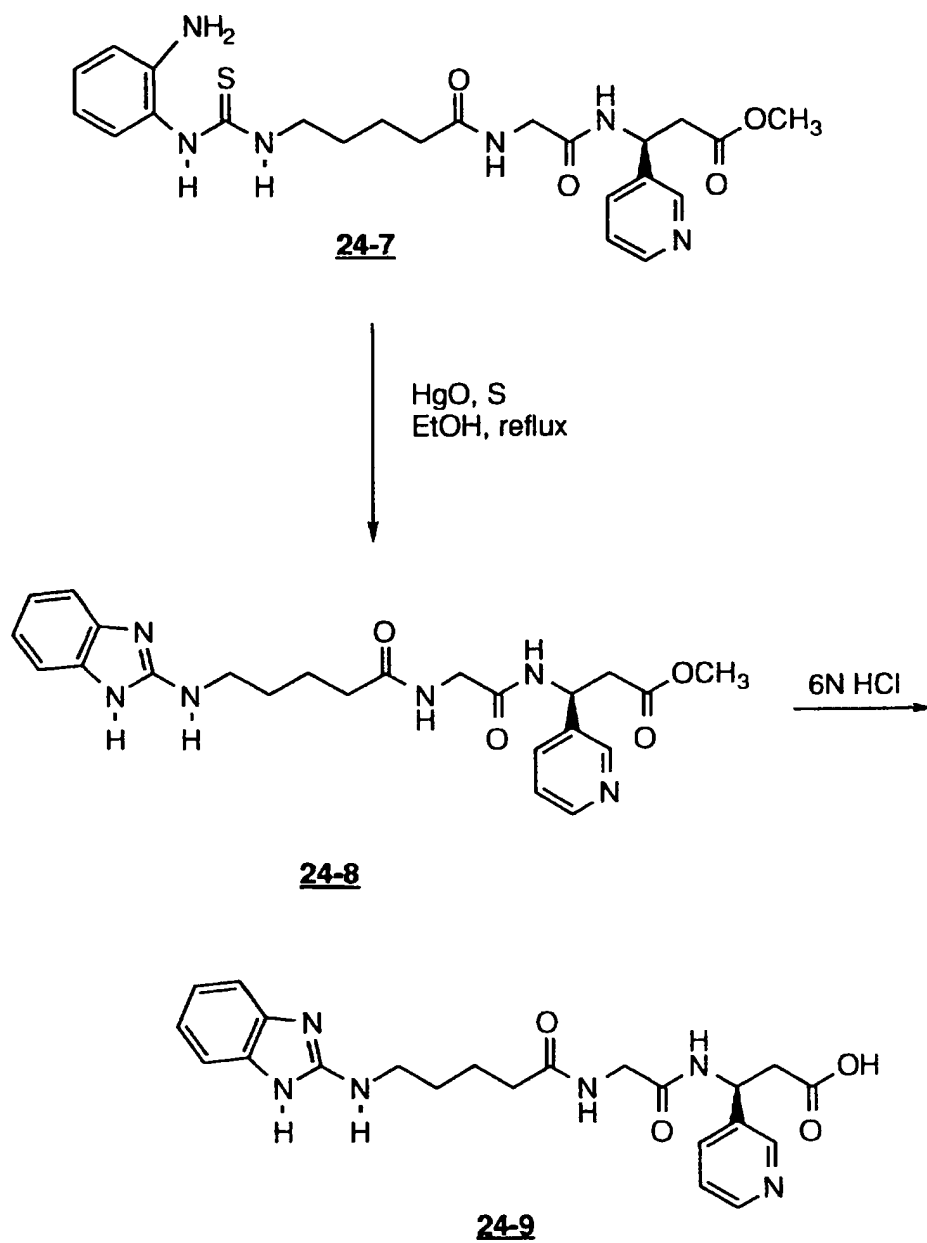
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SCHEME 24

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SCHEME 24 (CONT'D)

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SCHEME 24 (CONT'D)

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Preparation of 3-{2-[5-(1H-Benzoimidazol-2-yl-amino)-pentanoyl-amino]-acetylamino}-3(S)-pyridin-3-yl- propionic acid (24-9)

5 3-t-Butoxycarbonylaminoacetylamino-3(S)-pyridin-3-yl-propionic acid ethyl ester bis hydrochloride (24-1a)

A stirred solution of BOC-Gly (645 mg, 3.7 mmol), NMM (452 μ L, 4.0 mmol), and EtOAc (35 mL) at 0°C was treated with isobutyl chloroformate (534 μ L, 4.0 mmol). After 20 min 20-1 (1.0 g, 3.7 mmol) and NMM (1.2 mL, 11 mmol) were added followed by
10 removal of the cooling bath. After 20 hr, the reaction mixture was washed with H₂O, sat. NaHCO₃, and brine, dried (MgSO₄), and concentrated. Flash chromatography (silica, EtOAc to 5% MeOH/EtOAc) gave 24-1 as a colorless oil.

TLC: R_f = 0.31 (20% MeOH/EtOAc),
15 ¹H NMR (300MHz, CDCl₃) δ 8.58 (bs, 1H), 8.51(m, 1H), 7.62 (m, 1H), 7.49 (m, 1H), 5.48 (m, 1H), 4.13 (m, 1H), 4.08 (q, J=7Hz, 2H), 3.83 (m, 2H), 2.90 (m, 2H), 1.43 (s, 9H), 1.13 (t, J=7Hz, 3H).

20 3-Aminoacetylamino-3(S)-pyridin-3-yl-propionic acid ethyl ester bis-hydrochloride (24-2)

HCl gas was passed through a solution of 24-1a (0.84 g, 2.4 mmol) in EtOAc (24 mL) at 0°C for 15 min and the reaction mixture stirred for an additional 15 min. The reaction mixture was concentrated and the residue triturated with ether to give 24-2 as a white solid.

25 TLC: R_f = 0.29 (10:1:1 ethanol/H₂O/NH₄OH).

3-[2-(5-t-Butoxycarbonylamino)pentanoylamino]acetylamino]-3(S)-pyridin-3-yl-propionic acid ethyl ester (24-3)

A CH₃CN solution (20 mL) of 24-1 (71.7 mg, 0.33mmol),
30 24-2 (97 mg, 0.30 mmol), HOBT (50.5 mg, 0.33mmol), EDC (63.3 mg, 0.33 mmol) and NMM (132 mL, 1.2 mmol) was stirred under ambient conditions for 18 hr. The reaction solution was concentrated to a yellow gum which was partitioned between EtOAc and sat. NaCO₃

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solution. The EtOAc layer was washed with H₂O, brine, dried(MgSO₄) and concentrated to provide 24-3 as a colorless gum.

TLC: R_f = 0.41 (50% CH₂Cl₂/acetone),

¹H NMR (300MHz, CDCl₃) δ 8.56(bs, 1H), 8.51(m, 1H), 7.62(m, 1H),
5 7.49(m, 1H), 5.43(m, 1H), 4.08(q, J=7Hz, 2H), 3.94(m, 2H), 3.12(m,
2H), 2.90(m, 2H), 2.28(m, 2H), 1.64(m, 4H), 1.43(s, 9H), 1.13(t,
J=7Hz, 3H).

3-[2-(5-Aminopentanoylamino)-acetylamino]-3(S)-pyridin-3-yl-
10 propionic acid ethyl ester dihydrochloride (24-4)

A 4M HCl/dioxane solution(10 mL) of 24-3 (101 mg, 0.24 mmol) was stirred under ambient conditions for 18 hr. The solution was concentrated to provide 24-4 as a pale yellow gum which was used in the next step without further purification.

15 ¹H NMR (300 MHz, CD₃OD) δ 8.93(bs, 1H), 8.79(m, 1H), 8.69(m,
1H), 8.10(m, 1H), 5.48(m, 1H), 4.14(q, J=7Hz, 2H), 3.88(m, 2H),
3.07(m, 2H), 2.89(m, 2H), 2.33(m, 2H), 1.68(m, 4H), 1.23(t, J=7Hz,
3H).

20 3-(2-{5-[3-(2-Nitrophenyl)-thioureido]-pentanoylamino}-acetyl-
amino)-3(S)-pyridin-3-yl-propionic acid ethyl ester (24-6)

An ethanol solution(20 mL) of 24-5 (40 mg, 0.224 mmol) and 24-4 (95 mg, 0.224 mmol) was refluxed for 2 hr and concentrated to a yellow gum which was purified by flash chromatography (80%
25 EtOAc/EtOH-NH₃) to provide 24-6 as a yellow gum.

TLC: R_f = 0.41 (80% EtOAc/EtOH-NH₃),

¹H NMR (300 MHz, CD₃OD) δ 8.54(m, 1H), 8.42(m, 1H), 8.03(m,
2H), 7.83(m, 1H), 7.63(m, 1H), 7.41(m, 1H), 7.32(m, 1H), 5.39(m, 1H),
4.09(q, J=7 Hz, 2H), 3.86(s, 2H), 3.61(m, 2H), 2.91(m, 2H), 2.33(m,
30 2H), 1.69(m, 4H), 1.16(t, J=7Hz, 3H).

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3-(2-[5-[3-(2-Aminophenyl)-thioureido]-pentanoylamino]-
acetyl-amino)-3(S)-pyridin-3-yl-propionic acid methyl ester (24-7)

10% Pd/C (50 mg) and 24-6 (103 mg, 0.194 mmol) were added to methanol saturated with ammonia and the mixture

- 5 hydrogenated at 1 atm. for 18 hr. The reaction was filtered and concentrated to provide 24-7 as a pale yellow gum which was used in the next step without further purification.

¹H NMR (300MHz, CD₃OD) δ 8.53(m, 1H), 8.41(m, 1H), 7.84(m, 1H), 7.40(m, 1H), 7.07(m, 1H), 6.97(m, 1H), 6.82(m, 1H), 6.67(m, 1H),
10 5.38(m, 1H), 3.85(m, 2H), 3.62(s, 3H). 3.54(m, 2H), 2.93(m, 2H), 2.30(m, 2H), 1.60(m, 4H).

3-{2-[5-(1H-Benzoimidazol-2-yl-amino)-pentanoylamino]-acetyl-
amino)-3(S)-pyridin-3-yl-propionic acid methyl ester (24-8)

- 15 An ethanol mixture(20 ml) of 24-7 (89 mg, 0.18 mmol), mercuric oxide (78.8 mg, 0.36 mmol) and sulfur (1.8 mg, 0.056 mmol) was refluxed for 2 hr. After cooling, the mixture was filtered and the filtrate concentrated to a semi-solid which was purified by flash chromatography (20 % MeOH/CH₂Cl₂) to provide 24-8 as a solid.

20 TLC: R_f = 0.13 (20% MeOH/CH₂Cl₂),

¹H NMR (300 MHz, CD₃OD) δ 8.52(m, 1H), 8.41(m, 1H), 7.81(m, 1H), 7.38(m, 1H), 7.23(m, 2H), 7.06(m, 2H), 5.38(m, 1H), 3.85(s, 2H), 3.62(s, 3H), 3.37(m, 2H), 2.95(m, 2H), 2.33(m, 2H), 1.71(m, 4H).

- 25 3-{2-[5-(1H-Benzoimidazol-2-yl-amino)-pentanoylamino]-acetyl-
amino)-3(S)-pyridin-3-yl-propionic acid (24-9)

A 6N HCl solution (5 ml) of 24-8 (33 mg, 0.073 mmol) was stirred under ambient conditions for 18 hr. The reaction was concentrated to give a viscous gum which was purified by prep HPLC (Delta-Pak C₁₈, gradient elution over 40 min., 5-50% CH₃CN/H₂O-0.1% TFA) to give 24-9.

30 ¹H NMR (300MHz, CD₃OD) δ 8.78(m, 1H), 8.65(m, 1H), 8.40(m, 1H), 7.86(m, 1H), 7.34(m, 2H), 7.27(m, 2H), 5.40(m, 1H), 3.87(m, 2H), 3.42(m, 2H), 2.98(m, 2H), 2.34(m, 2H), 1.74(m, 4H).

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EXAMPLE 25

Tablet Preparation

5 Tablets containing 25.0, 50.0, and 100.0 mg., respectively, of the following active compounds are prepared as illustrated below:

4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine;

10

4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine; and

15 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine.

TABLE FOR DOSES CONTAINING
FROM 25-100MG OF THE ACTIVE COMPOUND

		<u>Amount-mg</u>	
Active Compound	25.0	50.0	100.0
Microcrystalline cellulose	37.25	100.0	200.0
Modified food corn starch	37.25	4.25	8.5
Magnesium stearate	0.50	0.75	1.5

20

25 All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 25.0, 50.0, and 100.0 mg, respectively, of active ingredient per tablet.

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EXAMPLE 26

Intravenous formulations

- 5 An intravenous dosage form of the above-indicated active compound is prepared as follows:

Active Compound	0.5-10.0mg
Sodium Citrate	5-50mg
Citric Acid	1-15mg
Sodium Chloride	1-8mg
Water for Injection (USP)	q.s. to 1 L

- 10 Utilizing the above quantities, the active compound is dissolved at room temperature in a previously prepared solution of sodium chloride, citric acid, and sodium citrate in Water for Injection (USP, see page 1636 of United States Pharmacopeia/National Formulary for 1995, published by United States Pharmacopeial Convention, Inc., Rockville, Maryland, copyright 1994.

15

EXAMPLE 27

Intravenous formulation

- 20 A pharmaceutical composition was prepared at room temperature using 4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester, a citrate buffer, and sodium chloride, to obtain a concentration of 4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester of 0.25 mg/ml.
- 25 800 grams of water was introduced into a standard pharmaceutical mixing vessel. 0.25 grams of the ester was dissolved in the water. 2.7 grams sodium citrate and 0.16 grams citric acid were added to obtain a finished citrate concentration of 10 mM. 8 grams of sodium chloride was added. 200 grams of water was then added to

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achieve the desired final concentrations of ingredients. The resulting aqueous formulation had the following concentrations:

	<u>Ingredient</u>	<u>Amount</u>
5	4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester	0.25 mg/ml
	citrate buffer	10 mM
10	sodium chloride	8 mg/ml

The finished concentrated formulation is stored in a standard USP Type I borosilicate glass container at 30-40 degrees C. Prior to compound administration, the concentrated formulation is
15 diluted in a 4:1 ratio resulting in a finished concentration of 0.05 mg/ml and transferred to an infusion bag.

Therapeutic Treatment

Compounds of the invention may be administered to
20 patients where inhibition of human or mammalian platelet aggregation or adhesion is desired.

Compounds of the invention are useful in inhibiting platelet aggregation and thus, they may find utility in surgery on peripheral arteries (arterial grafts, carotid endarterectomy) and in cardiovascular
25 surgery where manipulation of arteries and organs, and/or the interaction of platelets with artificial surfaces, leads to platelet aggregation and consumption. The aggregated platelets may form thrombi and thromboemboli. Compounds of the invention may be administered to these surgical patients to prevent the formation of thrombi and
30 thromboemboli.

Compounds of the invention are also effective inhibitors of osteoclast cellular adhesion, and can be administered to inhibit bone resorption. The dosage regimen utilizing the compounds of the present invention for this purpose is selected in accordance with a variety of

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factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the compounds, when used to prevent osteoclast cellular adhesion, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 100 mg/kg/day and preferably 0.01-50 mg/kg/day and more preferably 0.01-20 mg/kg/day, e.g. 0.1 mg/kg/day, 1.0 mg/kg/day, 5.0 mg/kg/day, or 10 mg/kg/day. Advantageously, compounds of the present invention may be administered in divided doses of two, three, or four times daily. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Furthermore, preferred compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, or course, be continuous rather than intermittent throughout the dosage regime.

EIB ASSAY

Duong *et al.*, *J. Bone Miner. Res.*, 8:S 378, describe a system for expressing the human integrin $\alpha_v\beta_3$. It has been suggested that the integrin is involved in the attachment of osteoclasts to bone matrix, since antibodies against the integrin, or RGD-containing molecules, such as echistatin (European Publication 382 451), can effectively block bone resorption.

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Reaction Mixture:

1. 175 μ l TBS buffer (50 mM Tris•HCl pH 7.2, 150 mM NaCl, 1% BSA, 1 mM CaCl₂, 1 mM MgCl₂).
 2. 25 μ l cell extract (dilute with 100 mM octylglucoside buffer to give 2000 cpm/25 μ l).
 3. ¹²⁵I-echistatin (25 μ l/50,000 cpm) (see EP 382 451).
 4. 25 μ l buffer (total binding) or unlabeled echistatin (non-specific binding).
- 10 The reaction mixture was then incubated for 1 h at room temp. The unbound and the bound $\alpha_v\beta_3$ were separated by filtration using a Skatron Cell Harvester. The filters (prewet in 1.5% poly-ethyleneimine for 10 mins) were then washed with the wash buffer (50 mM Tris HCl, 1mM CaCl₂/MgCl₂, pH 7.2). The filter was then
- 15 counted in a gamma counter.

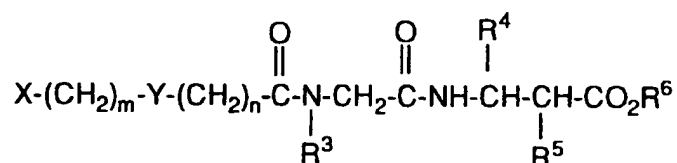
 The following compounds were tested and shown to bind to the human integrin $\alpha_v\beta_3$.

<u>Compound</u>	<u>EIB</u>
<u>2-3</u>	< 2000 nM
<u>3-8</u>	< 1000 nM
<u>5-9</u>	< 1000 nM
<u>19-10</u>	< 1000 nM
<u>20-3</u>	< 1000 nM
<u>24-9</u>	< 1000 nM

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WHAT IS CLAIMED IS:

1. A compound of the formula:



5 and pharmaceutically acceptable salts thereof, wherein
X is

a 5- or 6-membered monocyclic aromatic ring system containing
0, 1, 2, 3 or 4 heteroatoms selected from N, O and S and either
unsubstituted or substituted with R¹ or R², or

10

a 9- to 10-membered polycyclic ring system, wherein one or
more of the rings is aromatic, containing 0, 1, 2, 3 or 4
heteroatoms selected from N, O and S and either
unsubstituted or substituted with R¹ or R²,

15

wherein R¹ and R² are independently selected from the group
consisting of

hydrogen, F, Cl, Br, I,

C₁-10 alkyl,

20

C₃-8 cycloalkyl,

aryl,

aryl C₁-8 alkyl,

amino,

amino C₁-8 alkyl,

25

C₁-3 acylamino,

C₁-3 acylamino C₁-8 alkyl,

C₁-6 alkylamino,

C₁-6 alkylamino C₁-8 alkyl,

C₁-6 dialkylamino,

30

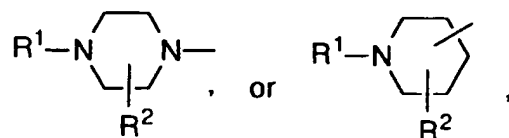
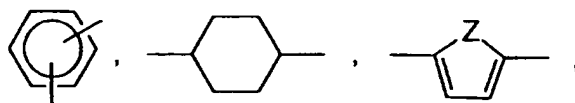
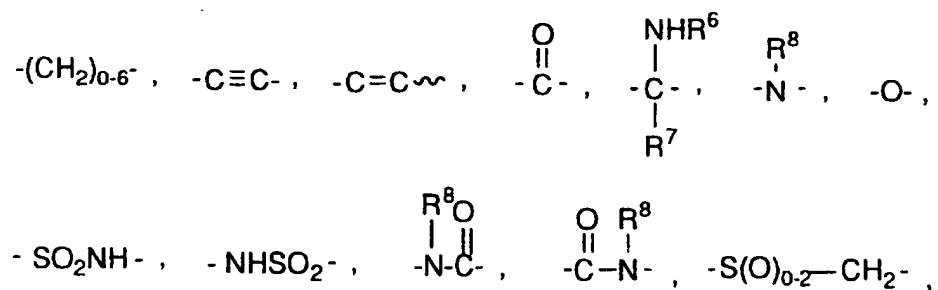
C₁-6 dialkylamino C₁-8 alkyl,

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C₁-4 alkoxy,
 C₁-4 alkoxy C₁-6 alkyl,
 carboxy,
 carboxy C₁-6 alkyl,
 5 C₁-3 alkoxy carbonyl,
 C₁-3 alkoxy carbonyl C₁-6 alkyl,
 carboxy C₁-6 alkyloxy and
 hydroxy,
 hydroxy C₁-6 alkyl;

10

Y is



where Z is O, NR⁸, or S; and R⁸ is defined as R¹ above;

R³ and R⁴ are independently
 hydrogen,

15 a five or six membered mono or polycyclic aromatic ring system
 containing 0, 1, 2, 3, or 4 heteroatoms selected from

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nitrogen, oxygen and sulfur, either unsubstituted or substituted, with one or more groups selected from hydroxyl, halogen, cyano, trifluoromethyl, C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅ alkoxy,
5 -(CH₂)_n-aryl, wherein n=1-4 and aryl is defined as a five or six membered mono or polycyclic aromatic ring system containing 0, 1, 2, 3, or 4 heteroatoms selected from
10 nitrogen, oxygen and sulfur, either unsubstituted or substituted, with one or more groups selected from hydroxyl, halogen, cyano, trifluoromethyl, C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₅
15 alkyl, or hydroxycarbonylC₁₋₅ alkoxy,
halogen,
hydroxyl,
C₁₋₅alkylcarbonylamino,
arylC₁₋₅ alkoxy,
20 C₁₋₅ alkoxy carbonyl,
aminocarbonyl,
C₁₋₅ alkylaminocarbonyl,
C₁₋₅ alkylcarbonyloxy,
C₃₋₈ cycloalkyl,
25 oxo,
amino,
C₁₋₃ alkylamino,
aminoC₁₋₃ alkyl,
arylaminocarbonyl,
30 arylC₁₋₅alkylaminocarbonyl,
aminocarbonyl,
aminocarbonyl-C₁₋₄ alkyl,
hydroxycarbonyl,
hydroxycarbonyl C₁₋₅ alkyl,

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- C₁₋₆alkyl, either unsubstituted or substituted, with one or more
 groups selected from halogen, hydroxyl,
 C₁₋₅alkylcarbonylamino, arylC₁₋₅ alkoxy,
 C₁₋₅ alkoxy carbonyl, aminocarbonyl,
 5 C₁₋₅ alkylaminocarbonyl,
 C₁₋₅ alkylcarbonyloxy, C₃₋₈ cycloalkyl, oxo, amino,
 C₁₋₃ alkylamino, aminoC₁₋₃ alkyl,
 arylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl,
 aminocarbonyl, aminocarbonyl-C₁₋₄ alkyl,
 10 hydroxycarbonyl, or hydroxycarbonyl C₁₋₅ alkyl,
 provided that the carbon atom to which R³ and R⁴ are
 attached bears only one heteroatom,
 -(CH₂)_m C≡CH,
 -(CH₂)_m C≡C-C₁₋₆ alkyl,
 15 -(CH₂)_m C≡C-C₃₋₇cycloalkyl,
 -(CH₂)_m C≡C- aryl,
 -(CH₂)_m C≡C-C₁₋₆ alkyl aryl,
 -(CH₂)_m CH=CH₂,
 -(CH₂)_m CH=CH C₁₋₆ alkyl,
 20 -(CH₂)_m CH=CH-C₃₋₇cycloalkyl,
 -(CH₂)_m CH=CH aryl,
 -(CH₂)_m CH=CH C₁₋₆ alkyl aryl,
 -(CH₂)_m SO₂C₁₋₆ alkyl, or
 -(CH₂)_m SO₂C₁₋₆ alkylaryl;
 25 R⁵ is
 hydrogen,
 fluorine,
 C₁₋₈ alkyl,
 30 hydroxyl,
 hydroxy C₁₋₆ alkyl,
 carboxy,
 carboxy C₁₋₆ alkyl,
 C₁₋₆ alkyloxy.

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- C3-8 cycloalkyl,
aryl C1-6 alkyloxy,
aryl,
aryl C1-6 alkyl,
5 C1-6 alkylcarbonyloxy,
amino,
amino C1-6 alkyl,
C1-6 alkylamino,
C1-6 alkylamino C1-6 alkyl,
10 aryl amino,
aryl amino C1-6 alkyl,
aryl C1-6 alkylamino,
aryl C1-6 alkylamino C1-6 alkyl,
aryl carbonyloxy,
15 aryl C1-6 alkylcarbonyloxy,
C1-6 dialkylamino,
C1-6 dialkylamino C1-6 alkyl,
C1-6 alkylaminocarbonyloxy,
C1-8 alkylsulfonylamino,
20 C1-8 alkylsulfonylamino C1-6 alkyl,
aryl sulfonylamino C1-6 alkyl,
aryl C1-6 alkylsulfonylamino,
aryl C1-6 alkylsulfonylamino C1-6 alkyl,
C1-8 alkyloxycarbonylamino,
25 C1-8 alkyloxycarbonylamino C1-8 alkyl,
aryl oxycarbonylamino C1-8 alkyl,
aryl C1-8 alkyloxycarbonylamino,
aryl C1-8 alkyloxycarbonylamino C1-8 alkyl,
C1-8 alkylcarbonylamino,
30 C1-8 alkylcarbonylamino C1-6 alkyl,
aryl carbonylamino C1-6 alkyl,
aryl C1-6 alkylcarbonylamino,
aryl C1-6 alkylcarbonylamino C1-6 alkyl,
aminocarbonylamino C1-6 alkyl,

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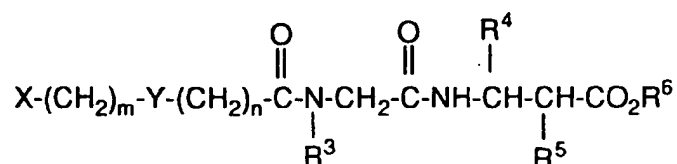
- C₁-8 alkylaminocarbonylamino,
- C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
- aryl aminocarbonylamino C₁-6 alkyl,
- aryl C₁-8 alkylaminocarbonylamino,
- 5 aryl C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
- aminosulfonylamino C₁-6 alkyl,
- C₁-8 alkylaminosulfonylamino,
- C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
- aryl aminosulfonylamino C₁-6 alkyl,
- 10 aryl C₁-8 alkylaminosulfonylamino,
- aryl C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
- C₁-6 alkylsulfonyl,
- C₁-6 alkylsulfonyl C₁-6alkyl,
- aryl sulfonyl C₁-6alkyl,
- 15 aryl C₁-6 alkylsulfonyl,
- aryl C₁-6 alkylsulfonyl C₁-6alkyl,
- C₁-6 alkylcarbonyl,
- C₁-6 alkylcarbonyl C₁-6 alkyl,
- aryl carbonyl C₁-6alkyl,
- 20 aryl C₁-6 alkylcarbonyl,
- aryl C₁-6 alkylcarbonyl C₁-6alkyl,
- C₁-6 alkylthiocarbonylamino,
- C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
- aryl thiocarbonylamino C₁-6 alkyl,
- 25 aryl C₁-6 alkylthiocarbonylamino,
- aryl C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
- aminocarbonyl C₁-6 alkyl, or
- C₁-8 alkylaminocarbonyl, or
- C₁-8 alkylaminocarbonyl C₁-6 alkyl, or
- 30 aryl aminocarbonyl C₁-6 alkyl,
- aryl C₁-8 alkylaminocarbonyl,
- aryl C₁-8 alkylaminocarbonyl C₁-6 alkyl,

wherein alkyl groups and aryl groups may be unsubstituted or substituted with one or more substituents selected from R¹ and R²; and

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- R⁶ and R⁷ are independently
hydrogen,
C₁₋₈ alkyl,
5 aryl,
aryl C₁₋₈ alkyl,
hydroxy,
C₁₋₈ alkyloxy,
aryloxy,
10 aryl C₁₋₆ alkyloxy,
C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
C₁₋₈ alkylaminocarbonylmethyleneoxy, or
C₁₋₈ dialkylaminocarbonylmethyleneoxy
15 where m and n are integers 0-6.

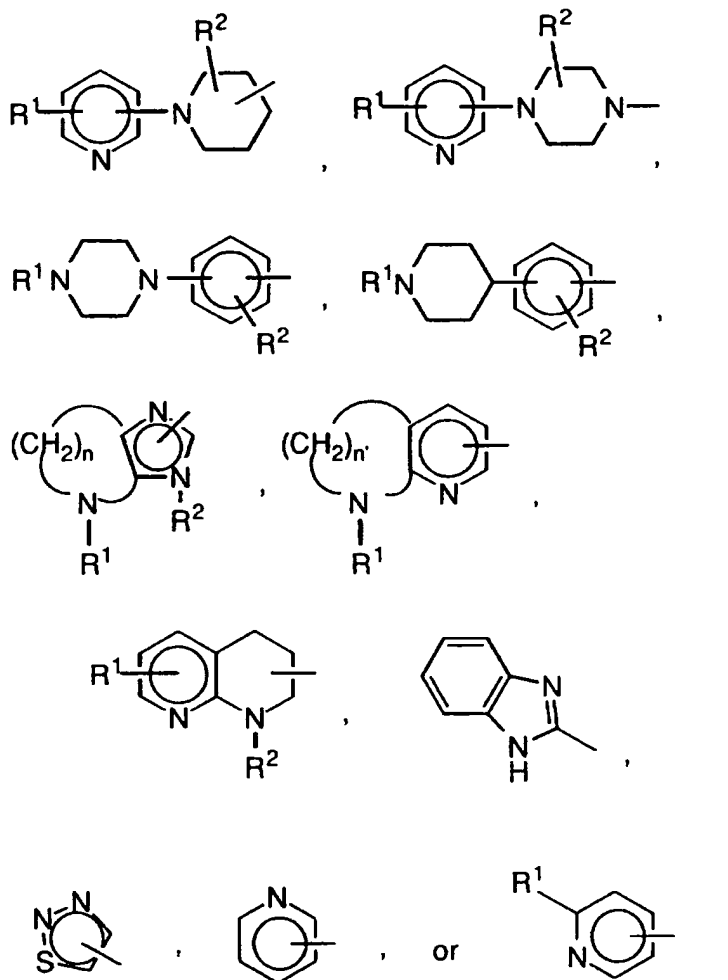
2. A compound of Claim 1 having the formula:



and pharmaceutically acceptable salts thereof, wherein

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X is



5

wherein n is 2-4, and n' is 2 or 3, and
 wherein R¹ and R² are independently selected from the group
 consisting of

10

hydrogen, F, Cl, Br, I,
 C₁-10 alkyl,
 C₃-8 cycloalkyl,
 aryl,
 aryl C₁-8 alkyl,
 amino,

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- 5 amino C₁₋₈ alkyl,
C₁₋₃ acylamino,
C₁₋₃ acylamino C₁₋₈ alkyl,
C₁₋₆ alkylamino,
C₁₋₆ alkylamino C₁₋₈ alkyl,
C₁₋₆ dialkylamino,
C₁₋₆ dialkylamino C₁₋₈ alkyl,
C₁₋₄ alkoxy,
C₁₋₄ alkoxy C₁₋₆ alkyl,
10 carboxy,
carboxy C₁₋₆ alkyl,
C₁₋₃ alkoxycarbonyl,
C₁₋₃ alkoxycarbonyl C₁₋₆ alkyl,
carboxy C₁₋₆ alkyloxy and
15 hydroxy,
hydroxy C₁₋₆ alkyl;

R⁵ is

- 20 hydrogen,
fluorine,
C₁₋₈ alkyl,
hydroxyl,
hydroxy C₁₋₆ alkyl,
carboxy,
25 carboxy C₁₋₆ alkyl,
C₁₋₆ alkyloxy.
C₃₋₈ cycloalkyl,
aryl C₁₋₆ alkyloxy,
aryl,
30 aryl C₁₋₆ alkyl,
C₁₋₆ alkylcarbonyloxy,
amino,
C₁₋₆ alkylamino,
amino C₁₋₆ alkyl,

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- C₁-6 alkylamino C₁-6 alkyl,
aryl amino,
aryl amino C₁-6 alkyl,
aryl C₁-6 alkylamino,
5 aryl C₁-6 alkylamino C₁-6 alkyl,
aryl carbonyloxy,
aryl C₁-6 alkylcarbonyloxy,
C₁-6 dialkylamino,
C₁-6 dialkylamino C₁-6 alkyl,
10 C₁-6 alkylaminocarbonyloxy,
C₁-8 alkylsulfonylamino,
C₁-8 alkylsulfonylamino C₁-6 alkyl,
aryl sulfonylamino C₁-6 alkyl,
aryl sulfonylamino,
15 aryl C₁-6 alkylsulfonylamino,
aryl C₁-6 alkylsulfonylamino C₁-6 alkyl,
C₁-8 alkyloxycarbonylamino,
C₁-8 alkyloxycarbonylamino C₁-8 alkyl,
aryl C₁-8 alkyloxycarbonylamino,
20 aryl oxycarbonylamino,
aryl oxycarbonylamino C₁-8 alkyl,
aryl C₁-8 alkyloxycarbonylamino C₁-8 alkyl,
C₁-8 alkylcarbonylamino,
C₁-8 alkylcarbonylamino C₁-6 alkyl,
25 aryl carbonylamino C₁-6 alkyl,
aryl carbonylamino,
aryl C₁-6 alkylcarbonylamino,
aryl C₁-6 alkylcarbonylamino C₁-6 alkyl,
C₁-8 alkylaminocarbonylamino,
30 aminocarbonylamino,
aminocarbonylamino C₁-6 alkyl,
C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
aryl aminocarbonylamino C₁-6 alkyl,
aryl aminocarbonylamino,

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- aryl C₁-8 alkylaminocarbonylamino,
aryl C₁-8 alkylaminocarbonylamino C₁-6 alkyl,
aminosulfonylamino C₁-6 alkyl,
aminosulfonylamino,
5 C₁-8 alkylaminosulfonylamino,
C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino C₁-6 alkyl,
aryl aminosulfonylamino,
aryl C₁-8 alkylaminosulfonylamino,
10 aryl C₁-8 alkylaminosulfonylamino C₁-6 alkyl,
C₁-6 alkylsulfonyl,
C₁-6 alkylsulfonyl C₁-6alkyl,
aryl sulfonyl,
aryl sulfonyl C₁-6alkyl,
15 aryl alkylsulfonyl,
aryl C₁-6 alkylsulfonyl,
aryl C₁-6 alkylsulfonyl C₁-6alkyl,
C₁-6 alkylcarbonyl,
C₁-6 alkylcarbonyl C₁-6 alkyl,
20 aryl carbonyl C₁-6alkyl,
aryl carbonyl,
aryl C₁-6 alkylcarbonyl,
aryl C₁-6 alkylcarbonyl C₁-6alkyl,
C₁-6 alkylthiocarbonylamino,
25 C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
aryl thiocarbonylamino C₁-6 alkyl,
aryl thiocarbonylamino,
aryl C₁-6 alkylthiocarbonylamino,
aryl C₁-6 alkylthiocarbonylamino C₁-6 alkyl,
30 aminocarbonyl C₁-6 alkyl,
aminocarbonyl,
C₁-8 alkylaminocarbonyl,
C₁-8 alkylaminocarbonyl C₁-6 alkyl,
aryl aminocarbonyl C₁-6 alkyl,

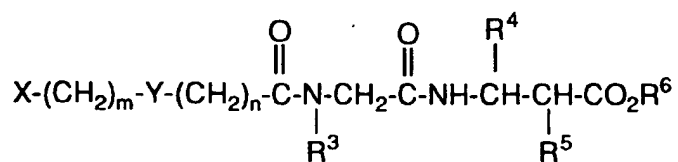
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aryl aminocarbonyl,
 aryl C₁-8 alkylaminocarbonyl,
 aryl C₁-8 alkylaminocarbonyl C₁-6 alkyl,
 wherein alkyl groups and aryl groups may be unsubstituted or
 5 substituted with one or more substituents selected from R¹ and R²; and

R⁶ and R⁷ are independently
 hydrogen,
 C₁-8 alkyl,
 10 aryl C₁-8 alkyl,
 hydroxy,
 C₁-8 alkyloxy,
 aryl,
 aryl C₁-6 alkyloxy,
 15 C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 aryl C₁-8 alkylcarbonyloxy C₁-4 alkyloxy,
 C₁-8 alkylaminocarbonylmethyleneoxy, or
 C₁-8 dialkylaminocarbonylmethyleneoxy,
 where m and n are integers 0-6.

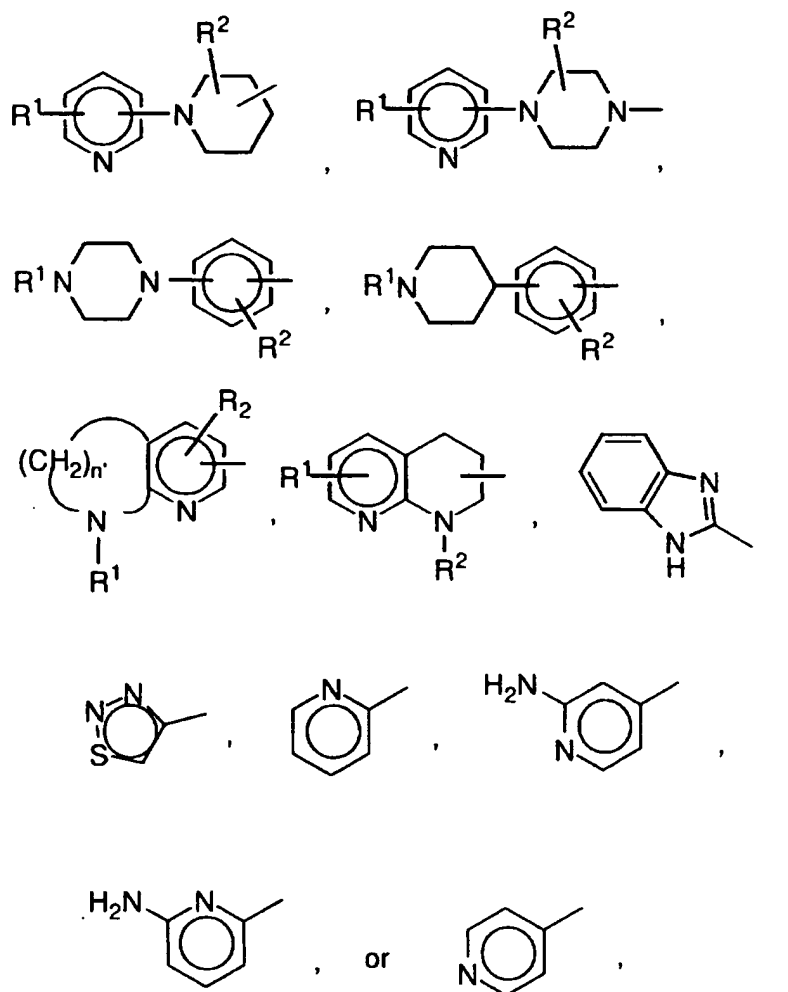
20

3. A compound of Claim 2 having the formula:



and pharmaceutically acceptable salts thereof, wherein
 X is

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wherein n' is 2 or 3, and

wherein R^1 and R^2 are independently selected from the group consisting of

hydrogen, F, Cl, Br, I,

C₁-10 alkyl,

C₃-8 cycloalkyl,

aryl,

aryl C₁-8 alkyl,

amino,

amino C₁-8 alkyl,

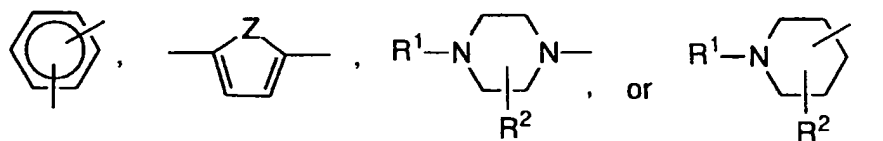
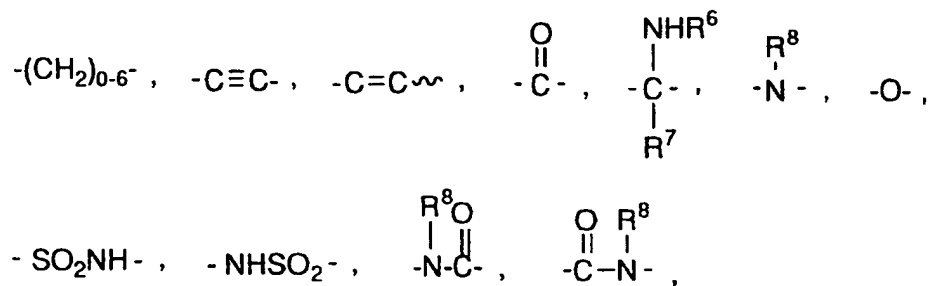
C₁-3 acylamino,

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C₁-3 acylamino C₁-8 alkyl,
 C₁-6 alkylamino,
 C₁-6 alkylamino C₁-8 alkyl,
 C₁-6 dialkylamino,
 C₁-6 dialkylamino C₁-8 alkyl,
 C₁-4 alkoxy,
 C₁-4 alkoxy C₁-6 alkyl,
 carboxy,
 carboxy C₁-6 alkyl,
 C₁-3 alkoxycarbonyl,
 C₁-3 alkoxycarbonyl C₁-6 alkyl,
 carboxy C₁-6 alkyloxy and
 hydroxy,
 hydroxy C₁-6 alkyl;

15

Y is



where Z is O, NR⁸, or S; and R⁸ is defined as R¹ above;

R³ and R⁴ are independently
 hydrogen,

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- a five or six membered mono or polycyclic aromatic ring system containing 0, 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen and sulfur, either unsubstituted or substituted, with one or more groups selected from
- 5 hydroxyl, halogen, cyano, trifluoromethyl, C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅ alkoxy,
- 10 $-(CH_2)_n$ -aryl, wherein n=1-4 and aryl is defined as a five or six membered mono or polycyclic aromatic ring system containing 0, 1, 2, 3, or 4 heteroatoms selected from nitrogen, oxygen and sulfur, either unsubstituted or substituted, with one or more groups selected from
- 15 hydroxyl, halogen, cyano, trifluoromethyl, C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl, C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅ alkoxy,
- halogen,
- hydroxyl,
- 20 C₁₋₅alkylcarbonylamino,
- arylC₁₋₅ alkoxy,
- C₁₋₅ alkoxy carbonyl,
- aminocarbonyl,
- C₁₋₅ alkylaminocarbonyl,
- 25 C₁₋₅ alkylcarbonyloxy,
- C₃₋₈ cycloalkyl,
- oxo,
- amino,
- C₁₋₃ alkylamino,
- 30 aminoC₁₋₃ alkyl,
- arylaminocarbonyl,
- arylC₁₋₅alkylaminocarbonyl,
- aminocarbonyl-C₁₋₄ alkyl,
- hydroxycarbonyl,

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- hydroxycarbonyl C₁₋₅ alkyl,
 C₁₋₆alkyl, either unsubstituted or substituted, with one or more
 groups selected from halogen, hydroxyl,
 C₁₋₅alkylcarbonylamino, arylC₁₋₅ alkoxy,
 5 C₁₋₅ alkoxycarbonyl, aminocarbonyl,
 C₁₋₅ alkylaminocarbonyl,
 C₁₋₅ alkylcarbonyloxy, C₃₋₈ cycloalkyl, oxo, amino,
 C₁₋₃ alkylamino, aminoC₁₋₃ alkyl,
 arylaminocarbonyl, arylC₁₋₅alkylaminocarbonyl,
 10 aminocarbonyl-C₁₋₄ alkyl, hydroxycarbonyl, or
 hydroxycarbonyl C₁₋₅ alkyl, provided that the carbon atom
 to which R³ and R⁴ are attached bears only one
 heteroatom,
 -(CH₂)_m C≡CH,
 15 -(CH₂)_m C≡C-C₁₋₆ alkyl,
 -(CH₂)_m C≡C-C₃₋₇cycloalkyl,
 -(CH₂)_m C≡C- aryl,
 -(CH₂)_m C≡C-C₁₋₆ alkyl aryl,
 -(CH₂)_m CH=CH₂,
 20 -(CH₂)_m CH=CH C₁₋₆ alkyl,
 -(CH₂)_m CH=CH-C₃₋₇cycloalkyl,
 -(CH₂)_m CH=CH aryl,
 -(CH₂)_m CH=CH C₁₋₆ alkyl aryl,
 -(CH₂)_mSO₂C₁₋₆alkyl, or
 25 -(CH₂)_mSO₂C₁₋₆ alkylaryl;

R⁵ is

- hydrogen,
 fluorine,
 30 C₁₋₈ alkyl,
 hydroxyl,
 hydroxy C₁₋₆ alkyl,
 carboxy,
 carboxy C₁₋₆ alkyl,

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- C₁-6 alkyloxy.
C₃-8 cycloalkyl,
aryl C₁-6 alkyloxy,
aryl C₁-6 alkyl,
5 C₁-6 alkylcarbonyloxy,
amino C₁-6 alkyl,
amino,
C₁-6 alkylamino,
C₁-6 alkylamino C₁-6 alkyl,
10 aryl amino C₁-6 alkyl,
aryl amino,
aryl C₁-6 alkylamino,
aryl C₁-6 alkylamino C₁-6 alkyl,
aryl,
15 aryl C₁-6 alkylcarbonyloxy,
C₁-6 dialkylamino,
C₁-6 dialkylamino C₁-6 alkyl,
C₁-6 alkylaminocarbonyloxy,
C₁-8 alkylsulfonylamino,
20 C₁-8 alkylsulfonylamino C₁-6 alkyl,
aryl sulfonylamino C₁-6 alkyl,
aryl sulfonylamino,
aryl C₁-6 alkylsulfonylamino,
aryl C₁-6 alkylsulfonylamino C₁-6 alkyl,
25 C₁-8 alkyloxycarbonylamino,
C₁-8 alkyloxycarbonylamino C₁-8 alkyl,
aryl oxycarbonylamino C₁-8 alkyl,
aryl oxycarbonylamino,
aryl C₁-8 alkyloxycarbonylamino,
30 aryl C₁-8 alkyloxycarbonylamino C₁-8 alkyl,
C₁-8 alkylcarbonylamino,
C₁-8 alkylcarbonylamino C₁-6 alkyl,
aryl carbonylamino C₁-6 alkyl,
aryl carbonylamino,

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- aryl C₁₋₆ alkylcarbonylamino,
aryl C₁₋₆ alkylcarbonylamino C₁₋₆ alkyl,
aminocarbonylamino C₁₋₆ alkyl,
aminocarbonylamino,
5 C₁₋₈ alkylaminocarbonylamino,
C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
aryl aminocarbonylamino C₁₋₆ alkyl,
aryl aminocarbonylamino,
aryl C₁₋₈ alkylaminocarbonylamino,
10 aryl C₁₋₈ alkylaminocarbonylamino C₁₋₆ alkyl,
aminosulfonylamino C₁₋₆ alkyl,
aminosulfonylamino,
C₁₋₈ alkylaminosulfonylamino,
C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
15 aryl aminosulfonylamino C₁₋₆ alkyl,
aryl aminosulfonylamino,
aryl C₁₋₈ alkylaminosulfonylamino,
aryl C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
C₁₋₆ alkylsulfonyl,
20 C₁₋₆ alkylsulfonyl C₁₋₆alkyl,
aryl sulfonyl C₁₋₆alkyl,
aryl sulfonyl,
aryl C₁₋₆ alkylsulfonyl,
aryl C₁₋₆ alkylsulfonyl C₁₋₆alkyl,
25 C₁₋₆ alkylcarbonyl,
C₁₋₆ alkylcarbonyl C₁₋₆ alkyl,
aryl carbonyl C₁₋₆alkyl,
aryl carbonyl,
aryl C₁₋₆ alkylcarbonyl,
30 aryl C₁₋₆ alkylcarbonyl C₁₋₆alkyl,
C₁₋₆ alkylthiocarbonylamino,
C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
aryl thiocarbonylamino C₁₋₆ alkyl,
aryl thiocarbonylamino,

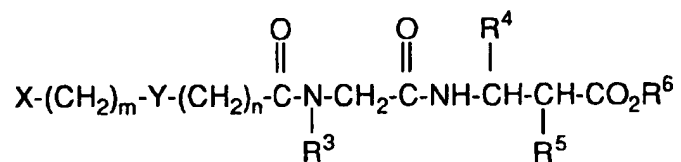
- 200 -

aryl C₁₋₆ alkylthiocarbonylamino,
aryl C₁₋₆ alkylthiocarbonylamino C₁₋₆ alkyl,
aminocarbonyl C₁₋₆ alkyl,
aminocarbonyl,
5 C₁₋₈ alkylaminocarbonyl,
C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
aryl aminocarbonyl C₁₋₆ alkyl,
aryl aminocarbonyl,
aryl C₁₋₈ alkylaminocarbonyl, or
10 aryl C₁₋₈ alkylaminocarbonyl C₁₋₆ alkyl,
wherein alkyl groups and aryl groups may be unsubstituted or
substituted with one or more substituents selected from R¹ and R²; and

R⁶ and R⁷ are independently
15 hydrogen,
C₁₋₈ alkyl,
aryl,
aryl C₁₋₈ alkyl,
hydroxy,
20 C₁₋₈ alkyloxy,
aryl oxy,
aryl C₁₋₆ alkyloxy,
C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
aryl C₁₋₈ alkylcarbonyloxy C₁₋₄ alkyloxy,
25 C₁₋₈ alkylaminocarbonylmethyleneoxy, or
C₁₋₈ dialkylaminocarbonylmethyleneoxy,
where m and n are integers 0-6.

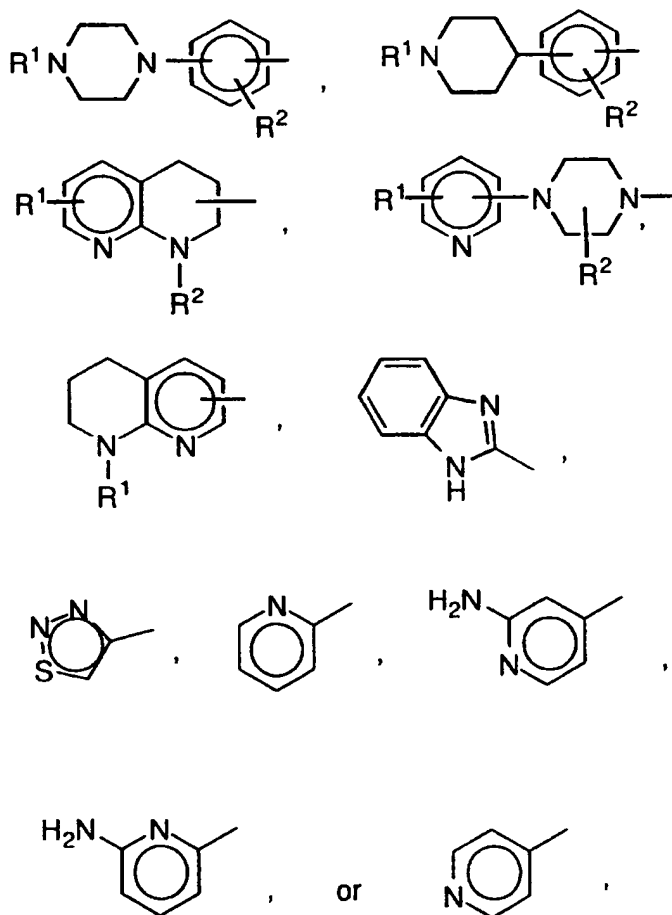
- 201 -

4. A compound of Claim 3 having the formula:



and pharmaceutically acceptable salts thereof, wherein

5 X is

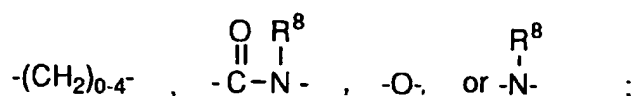


wherein R¹ and R² are independently selected from the group consisting of
hydrogen or
amino,

- 202 -

amino C₁₋₈ alkyl;

Y is

5 R⁸ is hydrogen or aryl C₀₋₈ alkyl;R³ is

hydrogen,

a six membered monocyclic aromatic ring system, either

10 unsubstituted or substituted, with one or more groups
selected from hydroxyl, halogen, cyano, trifluoromethyl,
C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl,
C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl,
hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅
alkoxy,

15 -(CH₂)_n-aryl, wherein n=1-4 and aryl is defined as a six
membered monocyclic aromatic ring system, either
unsubstituted or substituted, with one or more groups
selected from hydroxyl, halogen, cyano, trifluoromethyl,
C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl,
20 C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonyl,
hydroxycarbonylC₁₋₅ alkyl, or hydroxycarbonylC₁₋₅
alkoxy,

C₃₋₈ cycloalkyl, or

25 C₁₋₆alkyl, either unsubstituted or substituted, with C₃₋₈
cycloalkyl;

R⁴ is

hydrogen,

30 -(CH₂)_n-aryl, wherein n=0-4 and aryl is defined as a six
membered monocyclic aromatic ring system, either

unsubstituted or substituted, with one or more groups
selected from hydroxyl, halogen, cyano, trifluoromethyl,
C₁₋₃ alkoxy, C₁₋₅ alkylcarbonyloxy, C₁₋₅ alkoxy carbonyl,

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C₁₋₅ alkyl, aminoC₁₋₅ alkyl, hydroxycarbonylC₀₋₅ alkyl,
 or hydroxycarbonylC₁₋₅ alkoxy,
 C₁₋₆alkyl, or
 -(CH₂)₀₋₄ C≡CH;

5

R⁵ is

hydrogen,
 aryl sulfonylamino C₁₋₆ alkyl,
 aryl sulfonylamino,
 10 aryl C₁₋₆ alkylsulfonylamino,
 aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
 C₁₋₈ alkylsulfonylamino,
 C₁₋₈ alkylsulfonylamino C₁₋₆ alkyl,
 aryl sulfonylamino C₁₋₆ alkyl,
 15 aryl sulfonylamino,
 aryl C₁₋₆ alkylsulfonylamino,
 aryl C₁₋₆ alkylsulfonylamino C₁₋₆ alkyl,
 aminosulfonylamino C₁₋₆ alkyl,
 aminosulfonylamino,
 20 C₁₋₈ alkylaminosulfonylamino,
 C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
 aryl aminosulfonylamino C₁₋₆ alkyl,
 aryl aminosulfonylamino,
 aryl C₁₋₈ alkylaminosulfonylamino,
 25 aryl C₁₋₈ alkylaminosulfonylamino C₁₋₆ alkyl,
 C₁₋₆ alkylsulfonyl,
 C₁₋₆ alkylsulfonyl C₁₋₆alkyl,
 aryl sulfonyl C₁₋₆alkyl,
 aryl sulfonyl,
 30 aryl C₁₋₆ alkylsulfonyl,
 aryl C₁₋₆ alkylsulfonyl C₁₋₆alkyl,

wherein alkyl groups and aryl groups may be unsubstituted or
 substituted with one or more substituents selected from R₁ and R₂;

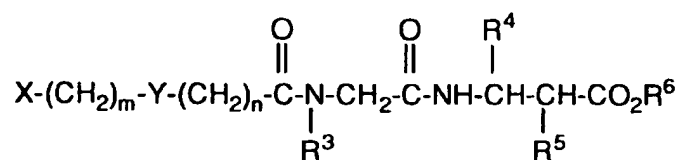
- 204 -

R6 is

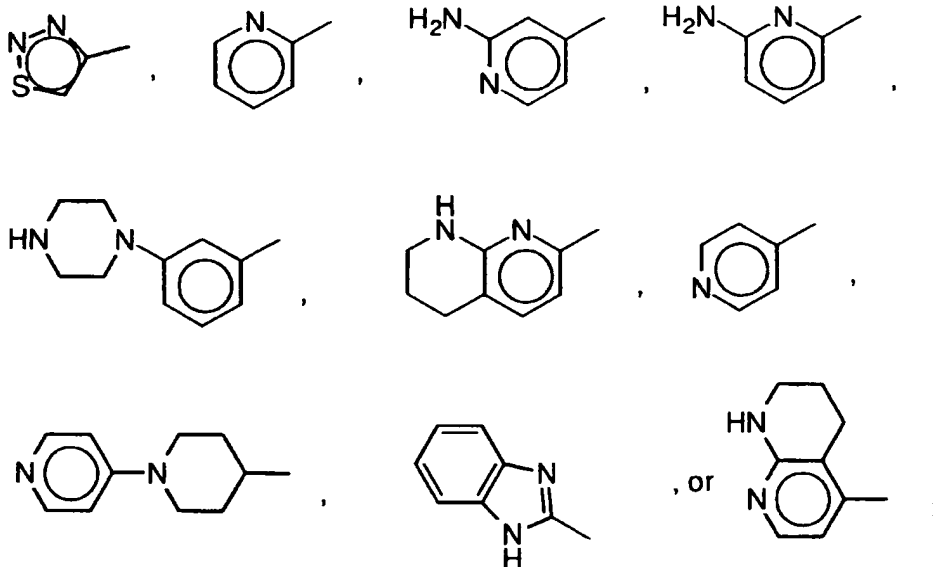
hydrogen,
C₁-8 alkyl, or
aryl,
aryl C₁-8 alkyl;

**m is an integer selected from 0 to 6; and
n is an integer selected from 0 to 6.**

10 5. A compound of Claim 4 having the formula:

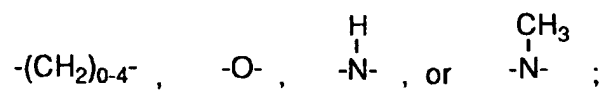


and pharmaceutically acceptable salts thereof, wherein X is

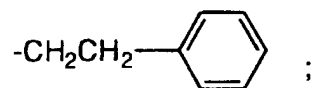


- 205 -

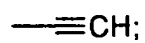
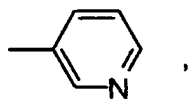
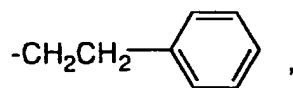
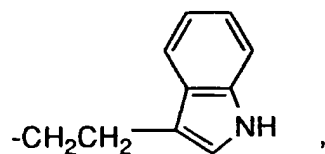
Y is

R³ is

5

hydrogen,
methyl,R⁴ is

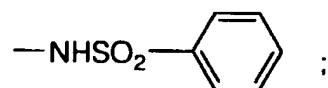
10

hydrogen,
methyl,

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R⁵ is

hydrogen, or

5 R⁶ is

hydrogen,
methyl,
ethyl, or
t-butyl;

10

m is an integer selected from 0 to 6; and
n is an integer selected from 0 to 6.

15 6. A compound of claim 5 selected from the group
consisting of

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido-β-alanine t-butyl ester,

20 4-(2-Aminothiazol-4-yl)butanoyl-glycyl-2(S)-phenylsulfonamido-β-alanine,

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)-β-alanine methyl ester,

25

4-(2-Aminothiazol-4-yl)butanoyl-glycyl-3(R)-(2-phenethyl)-β-alanine trifluoroacetate salt,

30 5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido-β-alanine ethyl ester,

5-(2-Pyridylamino)pentanoylglycyl-2(S)-phenylsulfonamido-β-alanine trifluoroacetate salt,

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4-(2-Bocamino-pyridin-6-yl)butanoyl-sarcosine-3(R)-[(2-indol-3-yl)ethyl]- β -alanine ethyl ester,

5 4-(2-Aminopyridin-6-yl)butanoyl-sarcosine-3(R)-[(2-indol-3-yl)ethyl]- β -alanine,

4-(2-Boc-aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine t-butyl ester,

10 4-(2-Aminopyridin-6-yl)butanoyl-glycyl-2(S)-phenylsulfonamido- β -alanine,

4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]- β -alanine ethyl ester,

15 4-(Pyridin-4-yl)butanoyl-sarcosine-3(R)-[2-(indol-3-yl)ethyl]- β -alanine,

4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester,

20 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester hydrochloride,

25 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-(2-phenethyl)- β -alanine,

4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine,

30 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-[(2-indol-3-yl)ethyl]- β -alanine,

4-(2-Bocamino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester,

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4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine ethyl ester,

5 4-(2-Amino-pyridin-6-yl)butanoyl-N-cyclopropylglycyl-3(R)-methyl- β -alanine,

4-(Pyridin-4-yl)butanoyl-N-(2-phenylethyl)glycyl-3(R)-(2-phenethyl)- β -alanine ethyl ester,

10 4-(Pyridin-4-yl)butanoyl-N-(2-phenyl)glycyl-3(R)-(2-phenethyl)- β -alanine,

4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine benzyl ester,

15 4-(2-BOC-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine,

20 4-(2-Aminopyridin-4-yl)butanoyl-N-(2-phenethyl)glycyl-3(R)-methyl- β -alanine,

4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine ethyl ester,

25 4-(Pyridyloxy)butyrate-N-(2-phenethyl)glycyl-3(R)-2-phenethyl- β -alanine,

3-[(N-Methyl)-N-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)- β -alanine ethyl ester,

30 3-[(N-Methyl)-N-(4-pyridyl)]aminopropionyl-sarcosine-3(R)-(2-phenethyl)- β -alanine,

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N-{N'-3-(4-t-Butoxycarbonyl-1-piperizinyl)benzoyl}glycyl}-3(R)-methyl- β -alanine benzyl ester,

5 N-[N'-[3-(1-Piperazinyl)benzoyl]glycyl]-3(R)-methyl- β -alanine trifluoroacetic acid salt,

N-[N'-[3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl]glycyl]-3(R)-(2-phenethyl)- β -alanine methyl ester,

10 N-[N'-[3-(1-Piperazinyl)benzoyl]glycyl]-3(R)-(2-phenethyl)- β -alanine trifluoroacetic acid salt,

15 N-[N'-[3-(4-t-Butoxycarbonyl-1-piperazinyl)benzoyl]-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)- β -alanine methyl ester,

N-[N'-[3-(1-Piperazinyl)benzoyl]-N'-(2-phenethyl)glycyl]-3(R)-(2-phenethyl)- β -alanine trifluoroacetic acid salt,

20 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl- β -alanine t-butyl ester,

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl- β -alanine,

25 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)-pyridin-3-yl- β -alanine ethyl ester,

30 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-7-yl)butanoyl-glycyl-3(S)-pyridin-3-yl- β -alanine,

Ethyl N-pyridin-4-ylisonipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine,

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N-Pyridin-ylisonipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine,

5 Ethyl N-pyridin-4-ylnipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine,

N-Pyridin-4-ylnipecotyl-N-cyclopropylglycyl-3(S)-ethynyl- β -alanine,

10 4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)-ethynyl- β -alanine ethyl ester,

4-(1,2,3,4-Tetrahydro-1,8-naphthyridin-5-yl)butanoyl-N-(cyclopropyl)glycyl-3(S)-ethynyl- β -alanine,

15 3-{2-[5-(1H-Benzoimidazol-2-yl-amino)-pentanoylamino]-acetylamino}-3(S)-pyridin-3-yl- propionic acid, and

and pharmaceutically acceptable salts thereof.

20

7. A compound of Claim 1 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.

25

8. A composition for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising an antifibrinogenic binding effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

30

9. A composition for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising an antifibrinogenic binding effective amount of a compound of Claim 1 and a pharmaceutically acceptable carrier.

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10. A composition for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising an antifibrinogenic binding effective amount of a compound of Claim 1 in combination with a thrombolytic agent and
5 a pharmaceutically acceptable carrier.

11. A composition for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising an antifibrinogenic binding effective amount
10 of a compound of Claim 1 in combination with an anticoagulant agent and pharmaceutically acceptable carrier.

12. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, comprising administering to the mammal a
15 composition of Claim 8.

13. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising administering to the mammal a composition of
20 Claim 9.

14. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising administering to the mammal a composition of
25 Claim 10.

15. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising administering to the mammal a composition of
30 Claim 11.

16. A composition for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising an antifibrinogenic binding effective amount

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of a compound of Claim 1 in combination with two or more agents selected from a thrombolytic agent, an anticoagulant agent, and an antiplatelet agent and a pharmaceutically acceptable carrier.

- 5 17. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising administering to the mammal the composition of Claim 16.
- 10 18. A compound of Claim 5 for use in inhibiting the binding of fibrinogen to blood platelets, inhibiting the aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal.
- 15 19. A composition for inhibiting the binding of fibrinogen to blood platelets, in a mammal, comprising an antifibrinogenic binding effective amount of a compound of Claim 6 and a pharmaceutically acceptable carrier.
- 20 20. A composition for inhibiting the aggregation of blood platelets, in a mammal, by blocking fibrinogen from acting at its receptor site, comprising an antifibrinogenic binding effective amount of a compound of Claim 6 and a pharmaceutically acceptable carrier.
- 25 21. A method for inhibiting the binding of fibrinogen to blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising administering to the mammal a composition of Claim 19.
- 30 22. A method for inhibiting the aggregation of blood platelets in a mammal, by blocking fibrinogen from acting at its receptor site, comprising administering to the mammal a composition of Claim 20.

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23. A composition for inhibiting osteoclast cellular adhesion to mammalian bone surfaces comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

5 24. A composition for inhibiting the solubilization of mammalian bone minerals by osteoclast cells in a mammal comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

10 25. A method for inhibiting osteoclast cellular adhesion to mammalian bone surfaces comprising treating the mammal with a pharmacologically effective amount of a composition of Claim 23.

15 26. A method for inhibiting the solubilization of mammalian bone minerals by osteoclast cells in a mammal comprising treating the mammal with a pharmacologically effective amount of a composition of Claim 24.

20 27. The use of a compound of Claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the aggregation of blood platelets, preventing platelet thrombosis, preventing thromboembolism or preventing reocclusion, in a mammal.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00572

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : CO7D 277/40; A61K 31/425

US CL : 548/195; 514/370

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 548/195; 514/370

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,553,227 A (WESTLAND) 05 JANUARY 1971(05/01/71), see entire document, especially column 1.	1-27, parts
A	US 4,684,722 A (SUNDEEN) 04 August 1987 (04/08/87), see entire document, especially column 1.	1-27, parts

☐

Further documents are listed in the continuation of Box C.

☐

See patent family annex.

*

Special categories of cited documents:

A

document defining the general state of the art which is not considered to be of particular relevance

E

earlier document published on or after the international filing date

L

document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O

document referring to an oral disclosure, use, exhibition or other means

P

document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

A

document member of the same patent family

Date of the actual completion of the international search

18 MARCH 1997

Date of mailing of the international search report

14 MAY 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ROBERT W. RAMSBERG

Telephone No. (703) -308-4534

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/00572

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-27, parts
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00572

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. X,Y,R1,R2,R3,R4,R5,Z,etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a CO-N-C-CO-N-C-C-CO group which does not define a contribution over the prior art. Therefore, the first discernable invention as found at page 48 (compound 1-8 therein, the pharmaceutical composition therewith, and the method of inhibiting the aggregation of blood platelets in a mammal therewith) has been searched.